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Management of chronic neuropathic pain: a protocol for a multiple treatment comparison meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Chronic neuropathic pain is associated with reduced health-related quality of life and substantial socioeconomic costs. Current research addressing management of chronic neuropathic pain is limited. No review has evaluated all interventional studies for chronic neuropathic pain, which limits attempts to make inferences regarding the relative effectiveness of treatments.

Methods and analysis: We will conduct a systematic review of all randomized controlled trials evaluating therapies for chronic neuropathic pain. We will identify eligible trials, in any language, by a systematic search of CINAHL, EMBASE, MEDLINE, AMED, HealthSTAR, DARE, PsychINFO, and the Cochrane Central Registry of Controlled Trials. Eligible trials will: (1) enrol patients presenting with chronic neuropathic pain, and (2) randomize patients to alternative interventions (pharmacological or non-pharmacological) or an intervention and a control arm. Pairs of reviewers will, independently and in duplicate, screen titles and abstracts of identified citations, review the full texts of potentially eligible trials, and extract information from eligible trials. We will use a modified Cochrane instrument to evaluate risk of bias of eligible studies, recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) to inform the outcomes we will collect, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate our confidence in treatment effects. When possible, we will conduct: (1) in direct comparisons, a random-effects meta-analyses to establish the

effect of reported therapies on patient-important outcomes; and (2) a multiple treatment comparison meta-analysis within a Bayesian framework to assess the relative effects of treatments. We will define *a priori* hypotheses to explain heterogeneity between studies, and conduct meta-regression and subgroup analyses consistent with current best practices.

Ethics and Dissemination: We do not require ethics approval for our proposed review. We will disseminate our findings through peer-reviewed publications and conference presentations.

Registration: PROSPERO (CRD42014009212).

STRENGTHS AND LIMITATIONS

- Our broad study eligibility criteria will allow us to generate more precise estimates of treatment effects, thus increasing generalizability of our results.

- We will use the GRADE approach to evaluate our confidence in treatment effects, and the IMMPACT guidelines to inform the outcomes we will collect. No existing review on the topic has done so.

- We will ensure interpretability by presenting both risk differences and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE Evidence Profiles. No existing review on the topic has done so.

- Our results will be limited by possible shortcomings of the primary studies.

BACKGROUND

Chronic neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.”[1] It may be classified as central or peripheral, depending on the site of the lesion.[2] Among the causes of chronic neuropathic pain are metabolic disease (e.g. diabetes), infection (e.g. shingles), trauma (e.g. spinal cord injury), and autoimmune disease (e.g. multiple sclerosis).[3-5] The pain may be spontaneous or evoked in response to physical stimuli. The latter may manifest as increased sensitivity to pain (hyperalgesia) or as a painful response to a stimulus that would not normally be painful (allodynia).[4, 6]

Chronic neuropathic pain is common worldwide, affecting 7% to 10% of the general population.[7] It is associated with depression, anxiety, and sleep disturbances, and patients with chronic neuropathic pain experience lower health-related quality of life than the general population.[8-11]

Chronic neuropathic pain is associated with substantial economic burden. Tarride et al. estimated that managing a Canadian patient with chronic neuropathic pain over a three-month period costs an average of $2,567, of which 52% are direct costs, e.g. cost of physicians, diagnostic tests, and surgical procedures.[12] Others report that people suffering from chronic neuropathic pain generate medical costs that are three times greater than those not living with pain.[11, 13] In the United States alone, almost $40

billion annually in health care, disability and related costs is attributed to chronic neuropathic pain.[4]

The underlying mechanisms of chronic neuropathic pain are poorly understood, which complicates management. Both non-pharmacological and pharmacological treatments are currently used. A limited number of systematic reviews focus on non-pharmacological options, including electrical nerve stimulation,[14] acupuncture,[15, 16] and cognitive behavioural therapy [17]. Most report pharmacological treatments for chronic neuropathic pain, including antidepressants,[18] anticonvulsants,[19] and opioid analgesics.[20]

Significant gaps remain though. For example, randomized controlled trials (RCTs) exploring treatment for chronic neuropathic pain often compare pharmacological treatments against placebo and seldom against each other. Consequently, there are few direct comparisons among treatments. A recent systematic review found that among 131 RCTs published between 1969 and 2007 and addressing painful diabetic neuropathy and postherpetic neuralgia, both common types of peripheral neuropathic pain, only 25 studies (19%) compared drugs directly against each other.[21]

Although systematic reviews have addressed management of chronic neuropathic pain, most focus on select therapies [18, 20, 22-45] or specific syndromes.[46-56] No review to date has systematically evaluated all evidence for management of chronic neuropathic pain. Additionally, risk of bias assessment of studies included in existing

reviews has been variable, and authors often depended on instruments that have been criticized for being overly simplistic (e.g. Jadad system) and/or assessed risk of bias on a per-study basis rather than overall for reported outcome.[57, 58] Furthermore, strategies to identify studies have been limited, as authors used few search terms, they did not search major literature databases, and/or they did not consider foreign language studies – an approach that would have excluded 12% of eligible trials in a systematic review of another chronic pain syndrome.[59] As well, none of the reviews employ the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the confidence in effect estimates (quality of evidence) for reported outcomes. And finally, none of the existing reviews facilitate interpretability, for instance, by presenting results in terms of minimally important differences (MID).

The limitations of previous works suggests the need for a new systematic review to be conducted using state-of-the-art methodology to inform evidence-based management of chronic neuropathic pain. We thus plan a systematic review and multiple treatment comparison meta-analysis of therapies for chronic neuropathic pain.

METHODS

Standardized Reporting

Our paper will conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews of RCTs.

Protocol Registration

Our protocol is registered on PROSPERO (registration number: CRD42014009212).

Search Strategy

We will identify relevant RCTs, in any language, by a systematic search of CINAHL, EMBASE, MEDLINE, AMED, HealthSTAR, DARE, PsychINFO, PapersFirst, ProceedingsFirst, and the Cochrane Central Registry of Controlled Trials, from the inception of each database. Our search will be refined for individual databases by a highly experienced medical librarian (RC) [Appendix 1 is a proposed search strategy for MEDLINE]. Reviewers will scan the bibliographies of all retrieved trials and other relevant publications, including reviews and meta-analyses, for additional relevant articles.

Eligibility criteria and their application to potentially eligible articles

Using standardized forms, reviewers trained in health research methodology will work in pairs to screen, independently and in duplicate, titles and abstracts of identified citations and acquire the full text publication of articles that both reviewers judge as potentially

eligible. Using a standardized form, the same reviewer teams will independently apply eligibility criteria to the full text of potentially eligible trials. We will measure agreement between reviewers to assess the reliability of full-text review using the guidelines proposed by Landis and Koch.[60] Specifically, we will calculate Kappa values, and interpret them using the following thresholds: <0.20 as slight agreement, 0.21-0.40 as fair agreement, 0.41-0.60 as moderate agreement, 0.61-0.80 as substantial agreement, and >0.80 as almost perfect agreement. Eligible trials will: (1) enrol patients presenting with chronic neuropathic pain [Appendix 2 lists all syndromes we are studying], and (2) randomize patients to alternative interventions (pharmacological or non-pharmacological) or to an intervention and control arm.

Data Abstraction and Analysis

Before starting data abstraction, we will conduct calibration exercises to ensure consistency between reviewers. Teams of reviewers will extract data independently and in duplicate from each eligible study using standardized forms and a detailed instruction manual to inform tailoring of an online data abstraction program, DistillerSR (http://systematic-review.net/). We will extract data regarding patient demographics, trial methodology, intervention details, and outcome data guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).[61, 62] Specifically, we will collect outcome data across the following nine IMMPACT-recommended core outcome domains: (1) pain; (2) physical functioning; (3) emotional functioning; (4) participant ratings of improvement and satisfaction with treatment; (5) symptoms and adverse events; (6) participation disposition; (7) role functioning; (8)

Interpersonal functioning; and (9) sleep and fatigue. We will collect data for all adverse outcomes as guided by Ioannidis and Lau.[63] We will resolve disagreements by discussion to achieve consensus.

Evaluating risk of bias in individual studies

Reviewers will assess risk of bias using a modified Cochrane risk of bias instrument that includes response options of "definitely or probably yes" – assigned a low risk of bias – or "definitely or probably no" – assigned a high risk of bias, an approach we have previously shown to be valid.[64] We will evaluate sequence generation, allocation sequence concealment; blinding of participants and study personnel; and, incomplete outcome data.[65] We will resolve any disagreements between reviewers by discussion. We will contact study authors if limitations in reporting lead to uncertainties in eligibility, risk of bias, or outcome.

Direct comparisons meta-analyses

In comparison to fixed effect models, random effect models are conservative in that they consider both within- and among-study variability. Recent methodological research has shown that while popular, the DerSimonian–Laird method [66] can produce narrow confidence intervals when the number of studies is small or when they are substantively heterogeneous.[67, 68] Therefore, to pool outcome data for trials that make direct comparisons between interventions and alternatives, we will use the likelihood profile approach.[69] We will pool cross-over trials with parallel design RCTs using methods outlined in the Cochrane handbook to derive effect estimates.[65] Specifically, we will

perform a paired t-test for each crossover trial if any of the following are available: (1) the individual participant data; (2) the mean and standard deviation (SD) or standard error (SE) of the participant-specific differences and between the intervention and control measurement; (3) the mean difference (MD) and one of the following: (i) a t-statistic from a paired t-test; (ii) a P value from a paired t-test; (iii) a confidence interval from a paired analysis; or (4) a graph of measurements of the intervention arm and control arm from which we can extract individual data values, so long as the matched measurement for each individual can be identified.[65] If these data are not available, we will approximate paired analyses by calculating the MDs and the corresponding SEs for the paired analyses.[65] If the SE or SD of within-participant differences are not available, we will impute the SD using the methods outlined in the Cochrane Handbook.[65]

Ensuring Interpretable Results

We will use a number of approaches to provide interpretable results from our meta-analyses. For studies that provide binary outcome measures, we will calculate relative risks (RRs) to inform relative effectiveness. To generate measures of absolute effect (risk differences), we will use estimates of baseline risk from the control arm of eligible RCTs.

When pooling across studies reporting continuous endpoints that use the same instrument, we will calculate the weighted mean difference (WMD), which maintains the original unit of measurement and represents the average difference between groups.

Once the WMD has been calculated, we will contextualize this value by noting the corresponding MID – the smallest change in instrument score that patients perceive is important. We will prioritize use of anchor-based MIDs when available, and calculate distribution-based MIDs when they are not. We will also divide WMDs by their corresponding MID to obtain estimates in MID units. However, contextualizing the WMD through the MID can be misleading; clinicians may mistakenly interpret any effect in MID units smaller than 1 as suggesting no patient obtains an important benefit, and any effect estimate greater than 1 as suggesting that all patients benefit, which is not accurate. Therefore, we will also calculate the proportion of patients who have benefited, i.e. demonstrated improvement greater than or equal to the MID in each trial, then aggregate the results across all studies.[70] Further, we will convert the proportion data to probabilities of experiencing benefit to calculate pooled RRs and numbers needed to treat (NNTs).

For trials that use different continuous outcome measures that address the same underlying construct, we will calculate the between-group difference in change scores (change from baseline) and divide this difference by the SD of the change. This calculation creates a measure of the effect (quantifying its magnitude in standard deviation units) called the standardized mean difference (SMD) that allows for comparison and pooling across trials.[65] However, the SMD is difficult to interpret and is vulnerable to the heterogeneity of patients that are enrolled: trials that enroll homogeneous study populations and thus have smaller standard deviations will generate a larger SMD than studies with more heterogeneous patient populations. To

address this issue, we will calculate the effect estimates in MID units by dividing between-group difference in change scores by the MID. However, as with WMDs, contextualizing the SMD in MID units can be misleading; therefore, we will, for each trial, calculate the probability of experiencing a treatment effect greater than or equal to the MID in the control and intervention groups, then pool the results to calculate RRs and NNTs.[70]

Assessment of heterogeneity and subgroup analyses

We will conduct conventional meta-analyses (see above) for each paired comparison. For each of these comparisons, we will examine heterogeneity using both a chi-squared test and the I^2 statistic – the percentage of variability that is due to true differences between studies (heterogeneity) rather than sampling error (chance).[71, 72]

We have generated five *a priori* hypotheses to explain variability between studies: (1) subjective syndromes will show smaller treatment effects versus objectively diagnosed syndromes; (2) trials comparing treatment to placebo will show larger treatment effects than trials using active comparators; (3) trials that exclude patients who are receiving disability benefits and/or involved in litigation will show larger treatment effects than trials that include such patients; (4) chronic neuropathic pain syndromes defined by peripheral nervous system lesions (e.g. diabetic neuropathy) will show larger effects that central nervous system lesions (e.g. chronic post-stroke pain); (5) trials with higher risk of bias will show larger treatment effects than trials with lower risk of bias; and, (6) trials with longer follow-up times will show smaller treatment effects than trials with

shorter follow-up times. To inform our subgroup analyses based on risk of bias we will, if we detect variability within the individual risk of bias components, perform subgroup analyses on a component-by-component basis. We will perform meta-regression and subgroup analyses to explore these hypotheses, and interpret the results in the context of the GRADE system (see below).[73]

Confidence in the estimates of effect

We will use the GRADE approach to evaluate confidence in effect estimates for all reported outcomes.[74] GRADE has been adopted by over 70 organizations worldwide, and this approach facilitates transparent, rigorous and comprehensive assessment of evidence quality on a per outcome basis.[75-88] Our review of the management of chronic neuropathic pain will be the first to use the GRADE criteria to evaluate confidence in effect estimates. We will categorize the confidence in estimates (quality of evidence) as high, moderate, low, or very low. Using this approach, randomized trials begin as high quality evidence but may be rated down by one or more of four categories of limitations. We will use GRADE guidance to determine whether to rate down confidence in the body of evidence for: (1) risk of bias;[86] (2) for imprecision; [80] for inconsistency;[82] and for publication bias.[83] For the risk of bias assessment, for any comparisons that suggest a statistically significant treatment effect, we will use recently developed approaches to address missing participant data for dichotomous outcomes and continuous outcomes.[89, 90] When plausible worst case scenarios reverse the treatment effect we will rate down for risk of bias. We will present the results of our

meta-analyses in GRADE Evidence Profiles that will provide a succinct, easily digestible presentation of the risk of bias and magnitude of effects.[74]

Multiple treatment comparison meta-analyses

To assess relative effects of competing treatments, we will construct a random effects model within the Bayesian framework using Markov chain Monte Carlo methods.[91] We will use trace plots and calculate the Gelman-Rubin statistic to assess model convergence. We will model patient-important outcomes in every treatment group of every study, and specify the relations among the effect sizes across studies.[92] This method combines direct and indirect evidence for any given pair of treatments. We will use the resulting 95% credible intervals (CrIs) to assess the precision of treatment effects.[93] A key assumption behind multiple treatment comparison meta-analysis is that the analysed network is consistent or coherent, i.e. that direct and indirect evidence on the same comparisons do not disagree beyond chance. We will identify and estimate incoherence by employing a mixed treatment comparisons incoherence model in the Bayesian framework.[94] For each comparison, we will note the direct estimates and associated CIs from the previous analysis and calculate the indirect estimate using a node splitting procedure as well as the network estimate. We will conduct a statistical test for incoherence between the direct and the indirect estimate.

We will have assessed confidence in estimates of effect from the direct comparisons in our pair-wise meta-analyses described previously. For rating confidence in the indirect comparisons, we will focus our assessments on first-order loops (that is, loops that are

connected to the interventions of interest through only one other intervention; for example A versus C and B versus C to estimate effects of A versus B) with the lowest variances, and thus contribute the most to the estimates of effect. Within each loop, our confidence in the indirect comparison will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. For instance, if treatment A versus C warrants high confidence and B versus C warrants moderate confidence, we will judge the associated indirect comparison (A versus B) as warranting moderate confidence. We may rate down confidence in the indirect comparisons further if we have a strong suspicion that the transitivity assumption (i.e. the assumption that there are no effect modifiers - such as differences in patients, extent to which interventions have been optimally administered, differences in the comparator, and differences in how the outcome has been measured - in the two direct comparisons that may bias the indirect estimate) has been violated.

Our overall judgement of confidence in the network estimate for any paired comparison will be the higher of the confidence rating amongst the contributing direct and indirect comparisons. However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates are incoherent.

As a secondary analysis, we will rank the interventions using the SUCRA (surface under the cumulative ranking) method.[95] The SUCRA rankings may be misleading if there is only evidence warranting low confidence for most comparisons; if the evidence supporting the higher ranked interventions warrants lower confidence than the evidence

supporting the lower ranked interventions; or if the magnitude of effect is very similar in higher versus lower ranked comparisons. We will consider these issues in interpreting the SUCRA rankings.

DISCUSSION

With the established high prevalence of chronic neuropathic pain worldwide, the associated high socioeconomic burden, and the paucity of evidence on the comparative effectiveness of treatment options, there is an urgent and critical need for a high-quality systematic review to inform evidence-based management of chronic neuropathic pain.

Our proposed review has several strengths in relation to existing reviews. First, we will include all non-pharmacological and pharmacological treatment options for all chronic neuropathic pain syndromes. It is plausible that individual pain syndromes, in general, respond similarly to similar interventions, and thus by pooling across individual syndromes, it may be possible to provide a more precise estimate of treatment effect. In addition, examining all therapies for all chronic neuropathic pain syndromes would provide comprehensive guidance for management of chronic neuropathic pain, which increases utility to health care providers, patients, and payers. Second, we will update the search to present date, explore a wider range of literature databases than existing reviews, and include eligible articles in all languages. Third, we will make all subjective decisions, including determining trial eligibility and collecting data, in teams of reviewers, independently and in duplicate, with assessments of the reproducibility of judgments. Fourth, we will focus on collecting patient-important outcomes across IMMPACT-recommended core domains. Fifth, we will use the GRADE approach to evaluate our confidence in treatment effects. Sixth, we will ensure interpretability by presenting both risk differences and measures of relative effect for all outcomes

reported, and by presenting our findings with GRADE Evidence Profiles. Seventh, we will generate a limited number of *a priori* subgroup hypotheses to explain heterogeneity of pooled estimates of treatment effect, and conduct meta-regression and subgroup analyses consistent with best current practices.

As with existing reviews, the results of our proposed systematic review will be limited by possible shortcomings of the primary studies, including presence of publication bias, high heterogeneity, and poor quality of reporting and methodological rigor. Another likely limitation, unique to multiple treatment comparison meta-analyses, will be the nature of available treatment comparisons to build robust networks for our analyses.

The findings of our review will help inform patients with chronic neuropathic pain about their therapeutic options, so that they can make more autonomous health management decisions. In addition, to help educate clinicians responsible for managing such patients, our review will facilitate updating clinical practice guidelines for the management of chronic neuropathic pain.

FOOTNOTES

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Competing Interests: DEM and AP are chair and member, respectively, of the Canadian Pain Society Guideline Committee for management of chronic neuropathic pain. DEM has received research grant funding from Pfizer Canada, and has received honoraria for educational presentations from Jansenn-Ortho, Lilly, Purdue Pharma and Merck-Frosst. All other authors report no conflicts of interest.

Acronyms: CrIs: Credible intervals; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; MD: Mean difference; MID: Minimally important difference; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs: Randomized controlled trials; RR: Relative risk; SD: Standard deviation; SE: Standard error; SMD: Standardized mean difference; SUCRA: surface under the cumulative ranking; WMD: Weighted mean difference

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Appendix 1: Proposed search strategy for MEDLINE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Search Strategy:

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11 peripheral nervous system diseases/ or brachial plexus neuropathies/ or brachial plexus neuritis/ or complex regional pain syndromes/ or causalgia/ or reflex sympathetic dystrophy/ or diabetic neuropathies/ or giant axonal neuropathy/ or guillain-barre syndrome/ or mononeuropathies/ or femoral neuropathy/ or median neuropathy/ or peroneal neuropathies/ or radial neuropathy/ or sciatic neuropathy/ or sciatica/ or tibial neuropathy/ or tarsal tunnel syndrome/ or ulnar neuropathies/ or cubital tunnel syndrome/ or ulnar nerve compression syndromes/ or nerve compression syndromes/ or carpal tunnel syndrome/ or piriformis muscle syndrome/ or pudendal neuralgia/ or thoracic outlet syndrome/ or cervical rib syndrome/ or neuralgia/ or neuralgia, postherpetic/ or neuritis/ or polyneuropathies/ or alcoholic neuropathy/ or "hereditary sensory and motor neuropathy"/ or alstrom syndrome/ or charcot-marie-tooth disease/ or refsum disease/ or spastic paraplegia, hereditary/ or poems syndrome/ or polyradiculoneuropathy/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or polyradiculopathy/ or radiculopathy/ (92706)
2 exp central nervous system disease/ (1143738)
3 "autoimmune diseases of the nervous system"/ or myelitis, transverse/ or neuromyelitis optica/ or polyradiculoneuropathy/ or guillain-barre syndrome/ or "hereditary sensory and autonomic neuropathies"/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ (10899)
4 Fabry Disease/ (2583)
5 Angiokeratoma/ (601)
6 Paraneoplastic Polyneuropathy/ (201)
7 Glossalgia/ (247)
8 Burning Mouth Syndrome/ (732)
9 Syringomyelia/ (3155)
10 Paroxysmal Hemicrania/ (75)
11 Trigeminal Autonomic Cephalalgias/ (105)
12 Phantom Limb/ (1528)
13 Thalamic Diseases/ (1103)
14 neuropath*.mp. (102493)
15 mononeuropath*.mp. (1492)
16 polyneuropath*.mp. (13247)
17 polyradiculoneuropath*.mp. (5027)
18 (Guillian adj Barre).mp. (87)
19 (Guillain adj Barre).mp. (7148)

20 (lewis adj sumner).mp. (49)
21 (charcot adj marie adj tooth).mp. (3790)
22 HMSN.mp. (432)
23 Peroneal muscular atrophy.mp. (165)
24 Guyon.ti,ab. (137)
25 Pronator teres.mp. (270)
26 (Struther$ adj ligament).mp. (18)
27 Wartenberg$.mp. (116)
28 Angiokeratoma.mp. (886)
29 (Anderson adj Fabry).mp. (208)
30 neuritis.mp. (13529)
31 neuronopath*.mp. (989)
32 myelinopath*.mp. (172)
33 distal axonopath*.mp. (229)
34 HIV-DSP.mp. (15)
35 Post-mastectomy pain.mp. (27)
36 Phantom limb.mp. (1828)
37 agnosia.mp. (2575)
38 plexopathy.mp. (723)
39 Radiculopathy.mp. (6164)
40 Glossodynia.mp. (136)
41 Stomatodynia.mp. (45)
42 (transverse adj myelitis).mp. (1338)
43 Fothergill*.mp. (75)
44 myelopath*.mp. (9661)
45 (Dejerine adj Roussy).mp. (37)
46 Syringomyelia.mp. (3784)
47 (Ramsay adj hunt).mp. (440)
48 (ramsey adj hunt).mp. (23)
49 sciatica.mp. (5358)
50 exp Multiple Sclerosis/ (44211)
51 exp Parkinsonian Disorders/ (58601)
52 parkinson.mp. (61412)
53 exp Stroke/ (85841)
54 (post adj stroke).mp. (3958)
55 thalamic*.mp. (24137)
56 exp Spinal Cord Injuries/ (37723)
57 cauda equina/ (2816)
58 cauda equina.mp. (4587)
59 exp Ophthalmoplegia/ (9669)
60 exp Herpes Zoster/ (9636)
61 postherpetic.mp. (1800)
62 Diabetic Neuropathies/ (12033)
63 small fiber.mp. (716)
64 exp HIV/ (84444)
65 hiv.mp. (275179)

66 or/1-65 (1625784)
67 neuropath*.mp. (102493)
68 neuralgi*.mp. (18296)
69 facial pain/ (5019)
70 phantom limb/ (1528)
71 phantom limb.mp. (1828)
72 CRPS.ti,ab. (1390)
73 CPSP.ti,ab. (157)
74 burning mouth syndrome/ (732)
75 dysesthe*.ti,ab. (1613)
76 (chronic adj2 pain).ti,ab. (31746)
77 pain measurement/ (60773)
78 or/67-77 (201452)
79 66 and 78 (119454)
80 Trigeminal Neuralgia/ (5540)
81 Facial Neuralgia/ (1121)
82 Facial Pain/ (5019)
83 Glossalgia/ (247)
84 Burning Mouth Syndrome/ (732)
85 Trigeminal Autonomic Cephalalgias/ (105)
86 neuralgia/ or neuralgia, postherpetic/ or piriformis muscle syndrome/ or pudendal neuralgia/ or sciatica/ (12818)
87 neuralgi*.mp. (18296)
88 Post-mastectomy pain.mp. (27)
89 postmastectomy pain syndrome.mp. (24)
90 PMPS.mp. (406)
91 Post-thoracotomy pain.mp. (234)
92 Phantom limb.mp. (1828)
93 agnosia.mp. (2575)
94 Glossodynia.mp. (136)
95 Stomatodynia.mp. (45)
96 (tic adj do?lo?re?ux?).mp. (300)
97 Prosopalgia.mp. (15)
98 meralgia paresthetica.mp. (277)
99 metatarsalgia.mp. (566)
100 (Ramsay adj hunt).mp. (440)
101 odontalgia.mp. (151)
102 sciatica.mp. (5358)
103 (Pain adj2 clinic).ti,ab. (1417)
104 (chronic adj2 pain).ti,ab. (31746)
105 (Neurogen* adj2 pain).ti,ab. (429)
106 low back pain/ (14091)
107 or/80-106 (77534)
108 79 or 107 (176257)
109 (dh or dt or pc or rh or rt or su or th).fs. (5395344)
110 exp Analgesia/ (31987)

111 exp Analgesics/ (433810)
112 analges*.mp. (140770)
113 treat*.mp. (4077132)
114 therap*.mp. (2410630)
115 intervention*.mp. (583724)
116 manag*.mp. (963377)
117 or/109-116 (8422296)
118 108 and 117 (104367)
119 randomized controlled trial.pt. (376906)
120 controlled clinical trial.pt. (88589)
121 randomized.ab. (297403)
122 placebo.ab. (155216)
123 drug therapy.fs. (1709609)
124 randomly.ab. (215113)
125 trial.ab. (308899)
126 groups.ab. (1367352)
127 or/119-126 (3364472)
128 exp animals/ not humans.sh. (3955572)
129 127 not 128 (2886355)
130 118 and 129 (36678)
131 limit 130 to "therapy (maximizes sensitivity)" (30615)
132 limit 131 to "review articles" (6311)
133 131 not 132 (24304)
134 Transcranial Magnetic Stimulation/ (6992)
135 rtms.mp. (2511)
136 magnetics/tu (807)
137 134 or 135 or 136 (8481)
138 pain.mp. (480976)
139 137 and 138 (542)
140 133 or 139 (24765)

Appendix 2: List of chronic neuropathic pain syndromes

- Central neuropathic pain
    - Parkinson disease-related pain
    - Compressive myelopathy from spinal stenosis
    - Post-traumatic spinal cord injury pain
    - Syringomyelia
    - HIV myelopathy
    - Multiple-sclerosis related pain
    - Post-ischemic myelopathy
    - Post-radiation myelopathy
    - Central post-stroke pain
        - Thalamic pain syndrome
        - Dejerine–Roussy syndrome
    - Transverse myelitis

- Peripheral neuropathic pain
    - Alcoholic neuropathy/polyneuropathy
    - Charcot-Marie-Tooth disease
        - Charcot-Marie-Tooth neuropathy
        - Hereditary motor and sensory neuropathy (HMSN)
        - Peroneal muscular atrophy (PMA)
    - Fabry disease (Fabry's disease, Anderson-Fabry disease, angiokeratoma corporis diffusum and alpha-galactosidase A deficiency)
    - Idiopathic sensory neuropathy
    - Nutritional deficiency-related neuropathies
        - Thiamine-deficiency neuropathy/beriberi neuropathy
    - Painful diabetic neuropathy
    - Abdominal migraine
    - Axillary neuropathy
    - Complex regional pain syndrome
        - Reflex sympathetic dystrophy
        - Causalgia
    - Entrapment neuropathies (nerve compression syndromes, compression neuropathy)
        - Anterior interosseous syndrome
        - Carpal tunnel syndrome
        - Cubital tunnel syndrome
        - Guyon's canal syndrome
        - Posterior interosseous neuropathy
        - Pronator teres syndrome
        - Radial neuropathy
        - Struthers' ligament syndrome
        - Wartenberg's Syndrome

- Nerve compression or infiltration by tumour
- Post-mastectomy pain
- Post-thoracotomy pain
- Post-surgical/post-operative neuropathic pain
- Phantom limb pain
- Radiculopathy (cervical, thoracic or lumbosacral)
- Post-traumatic neuralgia
- Meralgia paresthetica (neuropathy of the lateral femoral cutaneous nerve)
- Obturator neruralgia
- Femoral neuralgia
- Sciatic neuralgia
- Morton's neuralgia (interdigital metatarsalgia)
- Piriformis syndrome(technically a variation on sciatic)
- Cauda equina syndrome
- Post mastectomy pain is sometimes referred to (in the IASP taxonomy) as post mastectomypain syndrome
- Post thoracotomy pain syndrome
- Internal mammary artery syndrome (post cardiac surgery Internal Mammary nerve neuralgia)
- Segmental or intercostal neuralgia
- Abdominal cutaneous nerve entrapment syndrome
- Neuralgias of the genitofemoral, ilioinguinal, iliohypogastric, or pudendal nerves
- Facial nerves - neuralgias associated with each and every nerve including the branches of the trigeminal (V1-2-3); 7th nerve (Ramsay Hunt syndrome); glossopharyngeal nerve
- Occipital neuralgias
- Painful opthalmoplegia;
- Odontalgia
- Chronic paroxysmal hemicrania
- Thoracic outlet syndrome
- Acute and chronic inflammatory demyelinating polyradiculoneuropathy
  - Guillain–Barré syndrome
  - Lewis-Sumner syndrome
- Cancer-related neuropathy
  - Chemotherapy-induced peripheral neuropathy
  - Radiotherapy-induced peripheral neuropathy
- HIV-sensory neuropathy
  - HIV-associated distal sensory polyneuropathy (HIV-DSP)
- Postherpetic neuralgia
- Postradiation plexopathy
- Progressive inflammatory neuropathy
- Stomatodynia
  - Glossodynia
  - Burning mouth syndrome
- Toxic exposure-related neuropathies

- Trigeminal neuralgia (Tic douloureux)
  - Prosopalgia
  - Suicide disease
  - Fothergill's disease
- Vasculitic neuropathy
- Wartenberg's migratory sensory neuropathy

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Management of chronic neuropathic pain: a protocol for a multiple treatment comparison meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Chronic neuropathic pain is associated with reduced health-related quality of life and substantial socioeconomic costs. Current research addressing management of chronic neuropathic pain is limited. No review has evaluated all interventional studies for chronic neuropathic pain, which limits attempts to make inferences regarding the relative effectiveness of treatments.

Methods and analysis: We will conduct a systematic review of all randomized controlled trials evaluating therapies for chronic neuropathic pain. We will identify eligible trials, in any language, by a systematic search of CINAHL, EMBASE, MEDLINE, AMED, HealthSTAR, DARE, PsychINFO, and the Cochrane Central Registry of Controlled Trials. Eligible trials will: (1) enrol patients presenting with chronic neuropathic pain, and (2) randomize patients to alternative interventions (pharmacological or non-pharmacological) or an intervention and a control arm. Pairs of reviewers will, independently and in duplicate, screen titles and abstracts of identified citations, review the full texts of potentially eligible trials, and extract information from eligible trials. We will use a modified Cochrane instrument to evaluate risk of bias of eligible studies, recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) to inform the outcomes we will collect, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate our confidence in treatment effects. When possible, we will conduct: (1) in direct comparisons, a random-effects meta-analyses to establish the

effect of reported therapies on patient-important outcomes; and (2) a multiple treatment comparison meta-analysis within a Bayesian framework to assess the relative effects of treatments. We will define *a priori* hypotheses to explain heterogeneity between studies, and conduct meta-regression and subgroup analyses consistent with current best practices.

Ethics and Dissemination: We do not require ethics approval for our proposed review. We will disseminate our findings through peer-reviewed publications and conference presentations.

Registration: PROSPERO (CRD42014009212).

STRENGTHS AND LIMITATIONS

- Our broad study eligibility criteria will allow us to generate more precise estimates of treatment effects, thus increasing generalizability of our results.

- We will use the GRADE approach to evaluate our confidence in treatment effects, and the IMMPACT guidelines to inform the outcomes we will collect. No existing review on the topic has done so.

- We will ensure interpretability by presenting both risk differences and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE Evidence Profiles. No existing review on the topic has done so.

- Our results will be limited by possible shortcomings of the primary studies.

BACKGROUND

Chronic neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.”[1] It may be classified as central or peripheral, depending on the site of the lesion.[2] Among the causes of chronic neuropathic pain are metabolic disease (e.g. diabetes), infection (e.g. shingles), trauma (e.g. spinal cord injury), and autoimmune disease (e.g. multiple sclerosis).[3-5] The pain may be spontaneous or evoked in response to physical stimuli. The latter may manifest as increased sensitivity to pain (hyperalgesia) or as a painful response to a stimulus that would not normally be painful (allodynia).[4, 6]

Chronic neuropathic pain is common worldwide, affecting 7% to 10% of the general population.[7] It is associated with depression, anxiety, and sleep disturbances, and patients with chronic neuropathic pain experience lower health-related quality of life than the general population.[8-11]

Chronic neuropathic pain is associated with substantial economic burden. Tarride et al. estimated that managing a Canadian patient with chronic neuropathic pain over a three-month period costs an average of $2,567, of which 52% are direct costs, e.g. cost of physicians, diagnostic tests, and surgical procedures.[12] Others report that people suffering from chronic neuropathic pain generate medical costs that are three times greater than those not living with pain.[11, 13] In the United States alone, almost $40

billion annually in health care, disability and related costs is attributed to chronic neuropathic pain.[4]

The underlying mechanisms of chronic neuropathic pain are poorly understood, which complicates management. Both non-pharmacological and pharmacological treatments are currently used. A limited number of systematic reviews focus on non-pharmacological options, including electrical nerve stimulation,[14] acupuncture,[15, 16] and cognitive behavioural therapy [17]. Most report pharmacological treatments for chronic neuropathic pain, including antidepressants,[18] anticonvulsants,[19] and opioid analgesics.[20]

Significant gaps remain though. For example, randomized controlled trials (RCTs) exploring treatment for chronic neuropathic pain often compare pharmacological treatments against placebo and seldom against each other. Consequently, there are few direct comparisons among treatments. A recent systematic review found that among 131 RCTs published between 1969 and 2007 and addressing painful diabetic neuropathy and postherpetic neuralgia, both common types of peripheral neuropathic pain, only 25 studies (19%) compared drugs directly against each other.[21]

No review to date has systematically evaluated all evidence for management of chronic neuropathic pain; existing reviews focus on select therapies [18, 20, 22-46] or specific syndromes.[47-57] Additionally, risk of bias assessment of studies included in existing reviews has been variable, and authors often depended on instruments that have been

criticized for being overly simplistic (e.g. Jadad system) and/or assessed risk of bias on a per-study basis rather than overall for reported outcome.[58, 59] Furthermore, strategies to identify studies have been limited, as authors used few search terms, they did not search major literature databases, and/or they did not consider foreign language studies – an approach that would have excluded 12% of eligible trials in a systematic review of another chronic pain syndrome.[60] As well, none of the reviews employ the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the confidence in effect estimates (quality of evidence) for reported outcomes. And finally, none of the existing reviews facilitate interpretability, for instance, by presenting results in terms of minimally important differences (MID).

The limitations of previous works suggests the need for a new systematic review to be conducted using state-of-the-art methodology to inform evidence-based management of chronic neuropathic pain. We thus plan a systematic review and multiple treatment comparison meta-analysis of therapies for chronic neuropathic pain.

METHODS

Standardized Reporting

Our paper will conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews of RCTs.

Protocol Registration

Our protocol is registered on PROSPERO (registration number: CRD42014009212).

Search Strategy

We will identify relevant RCTs, in any language, by a systematic search of CINAHL, EMBASE, MEDLINE, AMED, HealthSTAR, DARE, PsychINFO, PapersFirst, ProceedingsFirst, and the Cochrane Central Registry of Controlled Trials, from the inception of each database. Our search will be refined for individual databases by a highly experienced medical librarian (RC) [Appendix 1 is a proposed search strategy for MEDLINE]. Reviewers will scan the bibliographies of all retrieved trials and other relevant publications, including reviews and meta-analyses, for additional relevant articles.

Eligibility criteria and their application to potentially eligible articles

Using standardized forms, reviewers trained in health research methodology will work in pairs to screen, independently and in duplicate, titles and abstracts of identified citations and acquire the full text publication of articles that both reviewers judge as potentially

eligible. Using a standardized form, the same reviewer teams will independently apply eligibility criteria to the full text of potentially eligible trials. We will measure agreement between reviewers to assess the reliability of full-text review using the guidelines proposed by Landis and Koch.[61] Specifically, we will calculate Kappa values, and interpret them using the following thresholds: <0.20 as slight agreement, 0.21-0.40 as fair agreement, 0.41-0.60 as moderate agreement, 0.61-0.80 as substantial agreement, and >0.80 as almost perfect agreement. Eligible trials will: (1) enrol patients presenting with chronic neuropathic pain [Appendix 2 lists all syndromes we are studying], and (2) randomize patients to alternative interventions (pharmacological or non-pharmacological) or to an intervention and control arm.

Data Abstraction and Analysis

Before starting data abstraction, we will conduct calibration exercises to ensure consistency between reviewers. Teams of reviewers will extract data independently and in duplicate from each eligible study using standardized forms and a detailed instruction manual to inform tailoring of an online data abstraction program, DistillerSR (http://systematic-review.net/). We will extract data regarding patient demographics, trial methodology, intervention details, and outcome data guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).[62, 63] Specifically, we will collect outcome data across the following nine IMMPACT-recommended core outcome domains: (1) pain; (2) physical functioning; (3) emotional functioning; (4) participant ratings of improvement and satisfaction with treatment; (5) symptoms and adverse events; (6) participation disposition; (7) role functioning; (8)

Interpersonal functioning; and (9) sleep and fatigue. We will collect data for all adverse outcomes as guided by Ioannidis and Lau.[64] We will resolve disagreements by discussion to achieve consensus.

Evaluating risk of bias in individual studies

Reviewers will assess risk of bias using a modified Cochrane risk of bias instrument that includes response options of "definitely or probably yes" – assigned a low risk of bias – or "definitely or probably no" – assigned a high risk of bias, an approach we have previously shown to be valid.[65] We will evaluate sequence generation, allocation sequence concealment; blinding of participants and study personnel; and, incomplete outcome data.[66] We will resolve any disagreements between reviewers by discussion. We will contact study authors if limitations in reporting lead to uncertainties in eligibility, risk of bias, or outcome.

Direct comparisons meta-analyses

In comparison to fixed effect models, random effect models are conservative in that they consider both within- and among-study variability. Recent methodological research has shown that while popular, the DerSimonian–Laird method [67] can produce narrow confidence intervals when the number of studies is small or when they are substantively heterogeneous.[68, 69] Therefore, to pool outcome data for trials that make direct comparisons between interventions and alternatives, we will use the likelihood profile approach.[70] We will pool cross-over trials with parallel design RCTs using methods outlined in the Cochrane handbook to derive effect estimates.[66] Specifically, we will

perform a paired t-test for each crossover trial if any of the following are available: (1) the individual participant data; (2) the mean and standard deviation (SD) or standard error (SE) of the participant-specific differences and between the intervention and control measurement; (3) the mean difference (MD) and one of the following: (i) a t-statistic from a paired t-test; (ii) a P value from a paired t-test; (iii) a confidence interval from a paired analysis; or (4) a graph of measurements of the intervention arm and control arm from which we can extract individual data values, so long as the matched measurement for each individual can be identified.[66] If these data are not available, we will approximate paired analyses by calculating the MDs and the corresponding SEs for the paired analyses.[66] If the SE or SD of within-participant differences are not available, we will impute the SD using the methods outlined in the Cochrane Handbook.[66]

Ensuring Interpretable Results

We will use a number of approaches to provide interpretable results from our meta-analyses. For studies that provide binary outcome measures, we will calculate relative risks (RRs) to inform relative effectiveness. To generate measures of absolute effect (risk differences), we will use estimates of baseline risk from the control arm of eligible RCTs.

When pooling across studies reporting continuous endpoints that use the same instrument, we will calculate the weighted mean difference (WMD), which maintains the original unit of measurement and represents the average difference between groups.

Once the WMD has been calculated, we will contextualize this value by noting the corresponding MID – the smallest change in instrument score that patients perceive is important. We will prioritize use of anchor-based MIDs when available, and calculate distribution-based MIDs when they are not. We will also divide WMDs by their corresponding MID to obtain estimates in MID units. However, contextualizing the WMD through the MID can be misleading; clinicians may mistakenly interpret any effect in MID units smaller than 1 as suggesting no patient obtains an important benefit, and any effect estimate greater than 1 as suggesting that all patients benefit, which is not accurate. Therefore, we will also calculate the proportion of patients who have benefited, i.e. demonstrated improvement greater than or equal to the MID in each trial, then aggregate the results across all studies.[71] Further, we will convert the proportion data to probabilities of experiencing benefit to calculate pooled RRs and numbers needed to treat (NNTs).

For trials that use different continuous outcome measures that address the same underlying construct, we will calculate the between-group difference in change scores (change from baseline) and divide this difference by the SD of the change. This calculation creates a measure of the effect (quantifying its magnitude in standard deviation units) called the standardized mean difference (SMD) that allows for comparison and pooling across trials.[66] However, the SMD is difficult to interpret and is vulnerable to the heterogeneity of patients that are enrolled: trials that enroll homogeneous study populations and thus have smaller standard deviations will generate a larger SMD than studies with more heterogeneous patient populations. To

address this issue, we will calculate the effect estimates in MID units by dividing between-group difference in change scores by the MID. However, as with WMDs, contextualizing the SMD in MID units can be misleading; therefore, we will, for each trial, calculate the probability of experiencing a treatment effect greater than or equal to the MID in the control and intervention groups, then pool the results to calculate RRs and NNTs.[71]

Patients may be interested in the ability of a given intervention to provide more than an MID – to produce improvement that allows patients to feel much better (i.e. substantially greater than the MID), Thus, for our analyses, for studies that report percentage reduction in pain, we will also use thresholds of ≥20%, ≥30% and ≥50% reduction of pain from baseline to calculate the proportion of patients who have benefited in each trial, and derive RRs and risk differences.

Assessment of heterogeneity and subgroup analyses

We will conduct conventional meta-analyses (see above) for each paired comparison. For each of these comparisons, we will examine heterogeneity using both a chi-squared test and the I^2 statistic – the percentage of variability that is due to true differences between studies (heterogeneity) rather than sampling error (chance).[72, 73]

We have generated five *a priori* hypotheses to explain variability between studies: (1) subjective syndromes will show smaller treatment effects versus objectively diagnosed syndromes; (2) trials comparing treatment to placebo will show larger treatment effects than trials using active comparators; (3) trials that exclude patients who are receiving

disability benefits and/or involved in litigation will show larger treatment effects than trials that include such patients; (4) chronic neuropathic pain syndromes defined by peripheral nervous system lesions (e.g. diabetic neuropathy) will show larger effects that central nervous system lesions (e.g. chronic post-stroke pain); (5) trials with higher risk of bias will show larger treatment effects than trials with lower risk of bias; and, (6) trials with longer follow-up times will show smaller treatment effects than trials with shorter follow-up times. To inform our subgroup analyses based on risk of bias we will, if we detect variability within the individual risk of bias components, perform subgroup analyses on a component-by-component basis. We will perform meta-regression and subgroup analyses to explore these hypotheses, and interpret the results in the context of the GRADE system (see below).[74]

Confidence in the estimates of effect

We will use the GRADE approach to evaluate confidence in effect estimates for all reported outcomes.[75] GRADE has been adopted by over 70 organizations worldwide, and this approach facilitates transparent, rigorous and comprehensive assessment of evidence quality on a per outcome basis.[76-89] Our review of the management of chronic neuropathic pain will be the first to use the GRADE criteria to evaluate confidence in effect estimates. We will categorize the confidence in estimates (quality of evidence) as high, moderate, low, or very low. Using this approach, randomized trials begin as high quality evidence but may be rated down by one or more of four categories of limitations. We will use GRADE guidance to determine whether to rate down confidence in the body of evidence for: (1) risk of bias;[87] (2) for imprecision; [81] for

inconsistency;[83] and for publication bias.[84] For the risk of bias assessment, for any comparisons that suggest a statistically significant treatment effect, we will use recently developed approaches to address missing participant data for dichotomous outcomes and continuous outcomes.[90, 91] When plausible worst case scenarios reverse the treatment effect we will rate down for risk of bias. We will present the results of our meta-analyses in GRADE Evidence Profiles that will provide a succinct, easily digestible presentation of the risk of bias and magnitude of effects.[75]

Multiple treatment comparison meta-analyses

To assess relative effects of competing treatments, we will construct a random effects model within the Bayesian framework using Markov chain Monte Carlo methods.[92] We will use trace plots and calculate the Gelman-Rubin statistic to assess model convergence. We will model patient-important outcomes in every treatment group of every study, and specify the relations among the effect sizes across studies.[93] This method combines direct and indirect evidence for any given pair of treatments. We will use the resulting 95% credible intervals (CrIs) to assess the precision of treatment effects.[94] A key assumption behind multiple treatment comparison meta-analysis is that the analysed network is consistent or coherent, i.e. that direct and indirect evidence on the same comparisons do not disagree beyond chance. We will identify and estimate incoherence by employing a mixed treatment comparisons incoherence model in the Bayesian framework.[95] For each comparison, we will note the direct estimates and associated CIs from the previous analysis and calculate the indirect estimate using a

node splitting procedure as well as the network estimate. We will conduct a statistical test for incoherence between the direct and the indirect estimate.

We will have assessed confidence in estimates of effect from the direct comparisons in our pair-wise meta-analyses described previously. For rating confidence in the indirect comparisons, we will focus our assessments on first-order loops (that is, loops that are connected to the interventions of interest through only one other intervention; for example A versus C and B versus C to estimate effects of A versus B) with the lowest variances, and thus contribute the most to the estimates of effect. Within each loop, our confidence in the indirect comparison will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. For instance, if treatment A versus C warrants high confidence and B versus C warrants moderate confidence, we will judge the associated indirect comparison (A versus B) as warranting moderate confidence. We may rate down confidence in the indirect comparisons further if we have a strong suspicion that the transitivity assumption (i.e. the assumption that there are no effect modifiers - such as differences in patients, extent to which interventions have been optimally administered, differences in the comparator, and differences in how the outcome has been measured - in the two direct comparisons that may bias the indirect estimate) has been violated.

Our overall judgement of confidence in the network estimate for any paired comparison will be the higher of the confidence rating amongst the contributing direct and indirect

comparisons. However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates are incoherent.

As a secondary analysis, we will rank the interventions using the SUCRA (surface under the cumulative ranking) method.[96] The SUCRA rankings may be misleading if there is only evidence warranting low confidence for most comparisons; if the evidence supporting the higher ranked interventions warrants lower confidence than the evidence supporting the lower ranked interventions; or if the magnitude of effect is very similar in higher versus lower ranked comparisons. We will consider these issues in interpreting the SUCRA rankings.

DISCUSSION

With the established high prevalence of chronic neuropathic pain worldwide, the associated high socioeconomic burden, and the paucity of evidence on the comparative effectiveness of treatment options, there is an urgent and critical need for a high-quality systematic review to inform evidence-based management of chronic neuropathic pain.

Our proposed review has several strengths in relation to existing reviews. First, we will include all non-pharmacological and pharmacological treatment options for all chronic neuropathic pain syndromes. It is plausible that individual pain syndromes, in general, respond similarly to similar interventions, and thus by pooling across individual syndromes, it may be possible to provide a more precise estimate of treatment effect. In addition, examining all therapies for all chronic neuropathic pain syndromes would provide comprehensive guidance for management of chronic neuropathic pain, which increases utility to health care providers, patients, and payers. Second, we will update the search to present date, explore a wider range of literature databases than existing reviews, and include eligible articles in all languages. Third, we will make all subjective decisions, including determining trial eligibility and collecting data, in teams of reviewers, independently and in duplicate, with assessments of the reproducibility of judgments. Fourth, we will focus on collecting patient-important outcomes across IMMPACT-recommended core domains. Fifth, we will use the GRADE approach to evaluate our confidence in treatment effects. Sixth, we will ensure interpretability by presenting both risk differences and measures of relative effect for all outcomes

reported, and by presenting our findings with GRADE Evidence Profiles. Seventh, we will generate a limited number of *a priori* subgroup hypotheses to explain heterogeneity of pooled estimates of treatment effect, and conduct meta-regression and subgroup analyses consistent with best current practices.

As with existing reviews, the results of our proposed systematic review will be limited by possible shortcomings of the primary studies, including presence of publication bias, high heterogeneity, and poor quality of reporting and methodological rigor. Another likely limitation, unique to multiple treatment comparison meta-analyses, will be the nature of available treatment comparisons to build robust networks for our analyses.

The findings of our review will help inform patients with chronic neuropathic pain about their therapeutic options, so that they can make more autonomous health management decisions. In addition, to help educate clinicians responsible for managing such patients, our review will facilitate updating clinical practice guidelines for the management of chronic neuropathic pain.

FOOTNOTES

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Competing Interests: DEM and AP are chair and member, respectively, of the Canadian Pain Society Guideline Committee for management of chronic neuropathic pain. DEM has received research grant funding from Pfizer Canada, and has received honoraria for educational presentations from Jansenn-Ortho, Lilly, Purdue Pharma and Merck-Frosst. All other authors report no conflicts of interest.

Acronyms: CrIs: Credible intervals; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; MD: Mean difference; MID: Minimally important difference; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs: Randomized controlled trials; RR: Relative risk; SD: Standard deviation; SE: Standard error; SMD: Standardized mean difference; SUCRA: surface under the cumulative ranking; WMD: Weighted mean difference

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Management of chronic neuropathic pain: a protocol for a multiple treatment comparison meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Chronic neuropathic pain is associated with reduced health-related quality of life and substantial socioeconomic costs. Current research addressing management of chronic neuropathic pain is limited. No review has evaluated all interventional studies for chronic neuropathic pain, which limits attempts to make inferences regarding the relative effectiveness of treatments.

Methods and analysis: We will conduct a systematic review of all randomized controlled trials evaluating therapies for chronic neuropathic pain. We will identify eligible trials, in any language, by a systematic search of CINAHL, EMBASE, MEDLINE, AMED, HealthSTAR, DARE, PsychINFO, and the Cochrane Central Registry of Controlled Trials. Eligible trials will: (1) enrol patients presenting with chronic neuropathic pain, and (2) randomize patients to alternative interventions (pharmacological or non-pharmacological) or an intervention and a control arm. Pairs of reviewers will, independently and in duplicate, screen titles and abstracts of identified citations, review the full texts of potentially eligible trials, and extract information from eligible trials. We will use a modified Cochrane instrument to evaluate risk of bias of eligible studies, recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) to inform the outcomes we will collect, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate our confidence in treatment effects. When possible, we will conduct: (1) in direct comparisons, a random-effects meta-analyses to establish the

effect of reported therapies on patient-important outcomes; and (2) a multiple treatment comparison meta-analysis within a Bayesian framework to assess the relative effects of treatments. We will define *a priori* hypotheses to explain heterogeneity between studies, and conduct meta-regression and subgroup analyses consistent with current best practices.

Ethics and Dissemination: We do not require ethics approval for our proposed review. We will disseminate our findings through peer-reviewed publications and conference presentations.

Registration: PROSPERO (CRD42014009212).

STRENGTHS AND LIMITATIONS

- Our broad study eligibility criteria will allow us to generate more precise estimates of treatment effects, thus increasing generalizability of our results.

- We will use the GRADE approach to evaluate our confidence in treatment effects, and the IMMPACT guidelines to inform the outcomes we will collect. No existing review on the topic has done so.

- We will ensure interpretability by presenting both risk differences and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE Evidence Profiles. No existing review on the topic has done so.

- Our results will be limited by possible shortcomings of the primary studies.

BACKGROUND

Chronic neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.”[1] It may be classified as central or peripheral, depending on the site of the lesion.[2] Among the causes of chronic neuropathic pain are metabolic disease (e.g. diabetes), infection (e.g. shingles), trauma (e.g. spinal cord injury), and autoimmune disease (e.g. multiple sclerosis).[3-5] The pain may be spontaneous or evoked in response to physical stimuli. The latter may manifest as increased sensitivity to pain (hyperalgesia) or as a painful response to a stimulus that would not normally be painful (allodynia).[4, 6]

Chronic neuropathic pain is common worldwide, affecting 7% to 10% of the general population.[7] It is associated with depression, anxiety, and sleep disturbances, and patients with chronic neuropathic pain experience lower health-related quality of life than the general population.[8-11]

Chronic neuropathic pain is associated with substantial economic burden. Tarride et al. estimated that managing a Canadian patient with chronic neuropathic pain over a three-month period costs an average of $2,567, of which 52% are direct costs, e.g. cost of physicians, diagnostic tests, and surgical procedures.[12] Others report that people suffering from chronic neuropathic pain generate medical costs that are three times greater than those not living with pain.[11, 13] In the United States alone, almost $40

billion annually in health care, disability and related costs is attributed to chronic neuropathic pain.[4]

The underlying mechanisms of chronic neuropathic pain are poorly understood, which complicates management. Both non-pharmacological and pharmacological treatments are currently used. A limited number of systematic reviews focus on non-pharmacological options, including electrical nerve stimulation,[14] acupuncture,[15, 16] and cognitive behavioural therapy [17]. Most report pharmacological treatments for chronic neuropathic pain, including antidepressants,[18] anticonvulsants,[19] and opioid analgesics.[20]

Significant gaps remain though. For example, randomized controlled trials (RCTs) exploring treatment for chronic neuropathic pain often compare pharmacological treatments against placebo and seldom against each other. Consequently, there are few direct comparisons among treatments. A recent systematic review found that among 131 RCTs published between 1969 and 2007 and addressing painful diabetic neuropathy and postherpetic neuralgia, both common types of peripheral neuropathic pain, only 25 studies (19%) compared drugs directly against each other.[21]

No review to date has systematically evaluated all evidence for management of chronic neuropathic pain; existing ~~Although systematic reviews have addressed management of chronic neuropathic pain, most~~reviews focus on select therapies [18, 20, 22-46] or specific syndromes.[47-57] ~~No review to date has systematically evaluated all evidence~~

for management of chronic neuropathic pain. Additionally, risk of bias assessment of studies included in existing reviews has been variable, and authors often depended on instruments that have been criticized for being overly simplistic (e.g. Jadad system) and/or assessed risk of bias on a per-study basis rather than overall for reported outcome.[58, 59] Furthermore, strategies to identify studies have been limited, as authors used few search terms, they did not search major literature databases, and/or they did not consider foreign language studies – an approach that would have excluded 12% of eligible trials in a systematic review of another chronic pain syndrome.[60] As well, none of the reviews employ the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the confidence in effect estimates (quality of evidence) for reported outcomes. And finally, none of the existing reviews facilitate interpretability, for instance, by presenting results in terms of minimally important differences (MID).

The limitations of previous works suggests the need for a new systematic review to be conducted using state-of-the-art methodology to inform evidence-based management of chronic neuropathic pain. We thus plan a systematic review and multiple treatment comparison meta-analysis of therapies for chronic neuropathic pain.

METHODS

Standardized Reporting

Our paper will conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting systematic reviews of RCTs.

Protocol Registration

Our protocol is registered on PROSPERO (registration number: CRD42014009212).

Search Strategy

We will identify relevant RCTs, in any language, by a systematic search of CINAHL, EMBASE, MEDLINE, AMED, HealthSTAR, DARE, PsychINFO, PapersFirst, ProceedingsFirst, and the Cochrane Central Registry of Controlled Trials, from the inception of each database. Our search will be refined for individual databases by a highly experienced medical librarian (RC) [Appendix 1 is a proposed search strategy for MEDLINE]. Reviewers will scan the bibliographies of all retrieved trials and other relevant publications, including reviews and meta-analyses, for additional relevant articles.

Eligibility criteria and their application to potentially eligible articles

Using standardized forms, reviewers trained in health research methodology will work in pairs to screen, independently and in duplicate, titles and abstracts of identified citations and acquire the full text publication of articles that both reviewers judge as potentially

eligible. Using a standardized form, the same reviewer teams will independently apply eligibility criteria to the full text of potentially eligible trials. We will measure agreement between reviewers to assess the reliability of full-text review using the guidelines proposed by Landis and Koch.[61] Specifically, we will calculate Kappa values, and interpret them using the following thresholds: <0.20 as slight agreement, 0.21-0.40 as fair agreement, 0.41-0.60 as moderate agreement, 0.61-0.80 as substantial agreement, and >0.80 as almost perfect agreement. Eligible trials will: (1) enrol patients presenting with chronic neuropathic pain [Appendix 2 lists all syndromes we are studying], and (2) randomize patients to alternative interventions (pharmacological or non-pharmacological) or to an intervention and control arm.

Data Abstraction and Analysis

Before starting data abstraction, we will conduct calibration exercises to ensure consistency between reviewers. Teams of reviewers will extract data independently and in duplicate from each eligible study using standardized forms and a detailed instruction manual to inform tailoring of an online data abstraction program, DistillerSR (http://systematic-review.net/). We will extract data regarding patient demographics, trial methodology, intervention details, and outcome data guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).[62, 63] Specifically, we will collect outcome data across the following nine IMMPACT-recommended core outcome domains: (1) pain; (2) physical functioning; (3) emotional functioning; (4) participant ratings of improvement and satisfaction with treatment; (5) symptoms and adverse events; (6) participation disposition; (7) role functioning; (8)

Interpersonal functioning; and (9) sleep and fatigue. We will collect data for all adverse outcomes as guided by Ioannidis and Lau.[64] We will resolve disagreements by discussion to achieve consensus.

Evaluating risk of bias in individual studies

Reviewers will assess risk of bias using a modified Cochrane risk of bias instrument that includes response options of "definitely or probably yes" – assigned a low risk of bias – or "definitely or probably no" – assigned a high risk of bias, an approach we have previously shown to be valid.[65] We will evaluate sequence generation, allocation sequence concealment; blinding of participants and study personnel; and, incomplete outcome data.[66] We will resolve any disagreements between reviewers by discussion. We will contact study authors if limitations in reporting lead to uncertainties in eligibility, risk of bias, or outcome.

Direct comparisons meta-analyses

In comparison to fixed effect models, random effect models are conservative in that they consider both within- and among-study variability. Recent methodological research has shown that while popular, the DerSimonian–Laird method [67] can produce narrow confidence intervals when the number of studies is small or when they are substantively heterogeneous.[68, 69] Therefore, to pool outcome data for trials that make direct comparisons between interventions and alternatives, we will use the likelihood profile approach.[70] We will pool cross-over trials with parallel design RCTs using methods outlined in the Cochrane handbook to derive effect estimates.[66] Specifically, we will

perform a paired t-test for each crossover trial if any of the following are available: (1) the individual participant data; (2) the mean and standard deviation (SD) or standard error (SE) of the participant-specific differences and between the intervention and control measurement; (3) the mean difference (MD) and one of the following: (i) a t-statistic from a paired t-test; (ii) a P value from a paired t-test; (iii) a confidence interval from a paired analysis; or (4) a graph of measurements of the intervention arm and control arm from which we can extract individual data values, so long as the matched measurement for each individual can be identified.[66] If these data are not available, we will approximate paired analyses by calculating the MDs and the corresponding SEs for the paired analyses.[66] If the SE or SD of within-participant differences are not available, we will impute the SD using the methods outlined in the Cochrane Handbook.[66]

Ensuring Interpretable Results

We will use a number of approaches to provide interpretable results from our meta-analyses. For studies that provide binary outcome measures, we will calculate relative risks (RRs) to inform relative effectiveness. To generate measures of absolute effect (risk differences), we will use estimates of baseline risk from the control arm of eligible RCTs.

When pooling across studies reporting continuous endpoints that use the same instrument, we will calculate the weighted mean difference (WMD), which maintains the original unit of measurement and represents the average difference between groups.

Once the WMD has been calculated, we will contextualize this value by noting the corresponding MID – the smallest change in instrument score that patients perceive is important. We will prioritize use of anchor-based MIDs when available, and calculate distribution-based MIDs when they are not. We will also divide WMDs by their corresponding MID to obtain estimates in MID units. However, contextualizing the WMD through the MID can be misleading; clinicians may mistakenly interpret any effect in MID units smaller than 1 as suggesting no patient obtains an important benefit, and any effect estimate greater than 1 as suggesting that all patients benefit, which is not accurate. Therefore, we will also calculate the proportion of patients who have benefited, i.e. demonstrated improvement greater than or equal to the MID in each trial, then aggregate the results across all studies.[71] Further, we will convert the proportion data to probabilities of experiencing benefit to calculate pooled RRs and numbers needed to treat (NNTs).

For trials that use different continuous outcome measures that address the same underlying construct, we will calculate the between-group difference in change scores (change from baseline) and divide this difference by the SD of the change. This calculation creates a measure of the effect (quantifying its magnitude in standard deviation units) called the standardized mean difference (SMD) that allows for comparison and pooling across trials.[66] However, the SMD is difficult to interpret and is vulnerable to the heterogeneity of patients that are enrolled: trials that enroll homogeneous study populations and thus have smaller standard deviations will generate a larger SMD than studies with more heterogeneous patient populations. To

address this issue, we will calculate the effect estimates in MID units by dividing between-group difference in change scores by the MID. However, as with WMDs, contextualizing the SMD in MID units can be misleading; therefore, we will, for each trial, calculate the probability of experiencing a treatment effect greater than or equal to the MID in the control and intervention groups, then pool the results to calculate RRs and NNTs.[71]

Patients may be interested in the ability of a given intervention to provide more than an MID – to produce improvement that allows patients to feel much better (i.e. substantially greater than the MID), Thus, for our analyses, for studies that report percentage reduction in pain, we will also use thresholds of ≥20%, ≥30% and ≥50% reduction of pain from baseline to calculate the proportion of patients who have benefited in each trial, and derive RRs and risk differences.

Assessment of heterogeneity and subgroup analyses

We will conduct conventional meta-analyses (see above) for each paired comparison. For each of these comparisons, we will examine heterogeneity using both a chi-squared test and the I^2 statistic – the percentage of variability that is due to true differences between studies (heterogeneity) rather than sampling error (chance).[72, 73]

We have generated five *a priori* hypotheses to explain variability between studies: (1) subjective syndromes will show smaller treatment effects versus objectively diagnosed syndromes; (2) trials comparing treatment to placebo will show larger treatment effects

than trials using active comparators; (3) trials that exclude patients who are receiving disability benefits and/or involved in litigation will show larger treatment effects than trials that include such patients; (4) chronic neuropathic pain syndromes defined by peripheral nervous system lesions (e.g. diabetic neuropathy) will show larger effects that central nervous system lesions (e.g. chronic post-stroke pain); (5) trials with higher risk of bias will show larger treatment effects than trials with lower risk of bias; and, (6) trials with longer follow-up times will show smaller treatment effects than trials with shorter follow-up times. To inform our subgroup analyses based on risk of bias we will, if we detect variability within the individual risk of bias components, perform subgroup analyses on a component-by-component basis. We will perform meta-regression and subgroup analyses to explore these hypotheses, and interpret the results in the context of the GRADE system (see below).[74]

Confidence in the estimates of effect

We will use the GRADE approach to evaluate confidence in effect estimates for all reported outcomes.[75] GRADE has been adopted by over 70 organizations worldwide, and this approach facilitates transparent, rigorous and comprehensive assessment of evidence quality on a per outcome basis.[76-89] Our review of the management of chronic neuropathic pain will be the first to use the GRADE criteria to evaluate confidence in effect estimates. We will categorize the confidence in estimates (quality of evidence) as high, moderate, low, or very low. Using this approach, randomized trials begin as high quality evidence but may be rated down by one or more of four categories of limitations. We will use GRADE guidance to determine whether to rate down

confidence in the body of evidence for: (1) risk of bias;[87] (2) for imprecision; [81] for inconsistency;[83] and for publication bias.[84] For the risk of bias assessment, for any comparisons that suggest a statistically significant treatment effect, we will use recently developed approaches to address missing participant data for dichotomous outcomes and continuous outcomes.[90, 91] When plausible worst case scenarios reverse the treatment effect we will rate down for risk of bias. We will present the results of our meta-analyses in GRADE Evidence Profiles that will provide a succinct, easily digestible presentation of the risk of bias and magnitude of effects.[75]

Multiple treatment comparison meta-analyses

To assess relative effects of competing treatments, we will construct a random effects model within the Bayesian framework using Markov chain Monte Carlo methods.[92] We will use trace plots and calculate the Gelman-Rubin statistic to assess model convergence. We will model patient-important outcomes in every treatment group of every study, and specify the relations among the effect sizes across studies.[93] This method combines direct and indirect evidence for any given pair of treatments. We will use the resulting 95% credible intervals (CrIs) to assess the precision of treatment effects.[94] A key assumption behind multiple treatment comparison meta-analysis is that the analysed network is consistent or coherent, i.e. that direct and indirect evidence on the same comparisons do not disagree beyond chance. We will identify and estimate incoherence by employing a mixed treatment comparisons incoherence model in the Bayesian framework.[95] For each comparison, we will note the direct estimates and associated CIs from the previous analysis and calculate the indirect estimate using a

node splitting procedure as well as the network estimate. We will conduct a statistical test for incoherence between the direct and the indirect estimate.

We will have assessed confidence in estimates of effect from the direct comparisons in our pair-wise meta-analyses described previously. For rating confidence in the indirect comparisons, we will focus our assessments on first-order loops (that is, loops that are connected to the interventions of interest through only one other intervention; for example A versus C and B versus C to estimate effects of A versus B) with the lowest variances, and thus contribute the most to the estimates of effect. Within each loop, our confidence in the indirect comparison will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. For instance, if treatment A versus C warrants high confidence and B versus C warrants moderate confidence, we will judge the associated indirect comparison (A versus B) as warranting moderate confidence. We may rate down confidence in the indirect comparisons further if we have a strong suspicion that the transitivity assumption (i.e. the assumption that there are no effect modifiers - such as differences in patients, extent to which interventions have been optimally administered, differences in the comparator, and differences in how the outcome has been measured - in the two direct comparisons that may bias the indirect estimate) has been violated.

Our overall judgement of confidence in the network estimate for any paired comparison will be the higher of the confidence rating amongst the contributing direct and indirect

comparisons. However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates are incoherent.

As a secondary analysis, we will rank the interventions using the SUCRA (surface under the cumulative ranking) method.[96] The SUCRA rankings may be misleading if there is only evidence warranting low confidence for most comparisons; if the evidence supporting the higher ranked interventions warrants lower confidence than the evidence supporting the lower ranked interventions; or if the magnitude of effect is very similar in higher versus lower ranked comparisons. We will consider these issues in interpreting the SUCRA rankings.

DISCUSSION

With the established high prevalence of chronic neuropathic pain worldwide, the associated high socioeconomic burden, and the paucity of evidence on the comparative effectiveness of treatment options, there is an urgent and critical need for a high-quality systematic review to inform evidence-based management of chronic neuropathic pain.

Our proposed review has several strengths in relation to existing reviews. First, we will include all non-pharmacological and pharmacological treatment options for all chronic neuropathic pain syndromes. It is plausible that individual pain syndromes, in general, respond similarly to similar interventions, and thus by pooling across individual syndromes, it may be possible to provide a more precise estimate of treatment effect. In addition, examining all therapies for all chronic neuropathic pain syndromes would provide comprehensive guidance for management of chronic neuropathic pain, which increases utility to health care providers, patients, and payers. Second, we will update the search to present date, explore a wider range of literature databases than existing reviews, and include eligible articles in all languages. Third, we will make all subjective decisions, including determining trial eligibility and collecting data, in teams of reviewers, independently and in duplicate, with assessments of the reproducibility of judgments. Fourth, we will focus on collecting patient-important outcomes across IMMPACT-recommended core domains. Fifth, we will use the GRADE approach to evaluate our confidence in treatment effects. Sixth, we will ensure interpretability by presenting both risk differences and measures of relative effect for all outcomes

reported, and by presenting our findings with GRADE Evidence Profiles. Seventh, we will generate a limited number of *a priori* subgroup hypotheses to explain heterogeneity of pooled estimates of treatment effect, and conduct meta-regression and subgroup analyses consistent with best current practices.

As with existing reviews, the results of our proposed systematic review will be limited by possible shortcomings of the primary studies, including presence of publication bias, high heterogeneity, and poor quality of reporting and methodological rigor. Another likely limitation, unique to multiple treatment comparison meta-analyses, will be the nature of available treatment comparisons to build robust networks for our analyses.

The findings of our review will help inform patients with chronic neuropathic pain about their therapeutic options, so that they can make more autonomous health management decisions. In addition, to help educate clinicians responsible for managing such patients, our review will facilitate updating clinical practice guidelines for the management of chronic neuropathic pain.

FOOTNOTES

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Competing Interests: DEM and AP are chair and member, respectively, of the Canadian Pain Society Guideline Committee for management of chronic neuropathic pain. DEM has received research grant funding from Pfizer Canada, and has received honoraria for educational presentations from Jansenn-Ortho, Lilly, Purdue Pharma and Merck-Frosst. All other authors report no conflicts of interest.

Acronyms: CrIs: Credible intervals; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials; MD: Mean difference; MID: Minimally important difference; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs: Randomized controlled trials; RR: Relative risk; SD: Standard deviation; SE: Standard error; SMD: Standardized mean difference; SUCRA: surface under the cumulative ranking; WMD: Weighted mean difference

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Appendix 1: Proposed search strategy for MEDLINE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

Search Strategy:

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11 peripheral nervous system diseases/ or brachial plexus neuropathies/ or brachial plexus neuritis/ or complex regional pain syndromes/ or causalgia/ or reflex sympathetic dystrophy/ or diabetic neuropathies/ or giant axonal neuropathy/ or guillain-barre syndrome/ or mononeuropathies/ or femoral neuropathy/ or median neuropathy/ or peroneal neuropathies/ or radial neuropathy/ or sciatic neuropathy/ or sciatica/ or tibial neuropathy/ or tarsal tunnel syndrome/ or ulnar neuropathies/ or cubital tunnel syndrome/ or ulnar nerve compression syndromes/ or nerve compression syndromes/ or carpal tunnel syndrome/ or piriformis muscle syndrome/ or pudendal neuralgia/ or thoracic outlet syndrome/ or cervical rib syndrome/ or neuralgia/ or neuralgia, postherpetic/ or neuritis/ or polyneuropathies/ or alcoholic neuropathy/ or "hereditary sensory and motor neuropathy"/ or alstrom syndrome/ or charcot-marie-tooth disease/ or refsum disease/ or spastic paraplegia, hereditary/ or poems syndrome/ or polyradiculoneuropathy/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or polyradiculopathy/ or radiculopathy/ (92706)
2 exp central nervous system disease/ (1143738)
3 "autoimmune diseases of the nervous system"/ or myelitis, transverse/ or neuromyelitis optica/ or polyradiculoneuropathy/ or guillain-barre syndrome/ or "hereditary sensory and autonomic neuropathies"/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ (10899)
4 Fabry Disease/ (2583)
5 Angiokeratoma/ (601)
6 Paraneoplastic Polyneuropathy/ (201)
7 Glossalgia/ (247)
8 Burning Mouth Syndrome/ (732)
9 Syringomyelia/ (3155)
10 Paroxysmal Hemicrania/ (75)
11 Trigeminal Autonomic Cephalalgias/ (105)
12 Phantom Limb/ (1528)
13 Thalamic Diseases/ (1103)
14 neuropath*.mp. (102493)
15 mononeuropath*.mp. (1492)
16 polyneuropath*.mp. (13247)
17 polyradiculoneuropath*.mp. (5027)
18 (Guillian adj Barre).mp. (87)
19 (Guillain adj Barre).mp. (7148)

20 (lewis adj sumner).mp. (49)
21 (charcot adj marie adj tooth).mp. (3790)
22 HMSN.mp. (432)
23 Peroneal muscular atrophy.mp. (165)
24 Guyon.ti,ab. (137)
25 Pronator teres.mp. (270)
26 (Struther$ adj ligament).mp. (18)
27 Wartenberg$.mp. (116)
28 Angiokeratoma.mp. (886)
29 (Anderson adj Fabry).mp. (208)
30 neuritis.mp. (13529)
31 neuronopath*.mp. (989)
32 myelinopath*.mp. (172)
33 distal axonopath*.mp. (229)
34 HIV-DSP.mp. (15)
35 Post-mastectomy pain.mp. (27)
36 Phantom limb.mp. (1828)
37 agnosia.mp. (2575)
38 plexopathy.mp. (723)
39 Radiculopathy.mp. (6164)
40 Glossodynia.mp. (136)
41 Stomatodynia.mp. (45)
42 (transverse adj myelitis).mp. (1338)
43 Fothergill*.mp. (75)
44 myelopath*.mp. (9661)
45 (Dejerine adj Roussy).mp. (37)
46 Syringomyelia.mp. (3784)
47 (Ramsay adj hunt).mp. (440)
48 (ramsey adj hunt).mp. (23)
49 sciatica.mp. (5358)
50 exp Multiple Sclerosis/ (44211)
51 exp Parkinsonian Disorders/ (58601)
52 parkinson.mp. (61412)
53 exp Stroke/ (85841)
54 (post adj stroke).mp. (3958)
55 thalamic*.mp. (24137)
56 exp Spinal Cord Injuries/ (37723)
57 cauda equina/ (2816)
58 cauda equina.mp. (4587)
59 exp Ophthalmoplegia/ (9669)
60 exp Herpes Zoster/ (9636)
61 postherpetic.mp. (1800)
62 Diabetic Neuropathies/ (12033)
63 small fiber.mp. (716)
64 exp HIV/ (84444)
65 hiv.mp. (275179)

66 or/1-65 (1625784)
67 neuropath*.mp. (102493)
68 neuralgi*.mp. (18296)
69 facial pain/ (5019)
70 phantom limb/ (1528)
71 phantom limb.mp. (1828)
72 CRPS.ti,ab. (1390)
73 CPSP.ti,ab. (157)
74 burning mouth syndrome/ (732)
75 dysesthe*.ti,ab. (1613)
76 (chronic adj2 pain).ti,ab. (31746)
77 pain measurement/ (60773)
78 or/67-77 (201452)
79 66 and 78 (119454)
80 Trigeminal Neuralgia/ (5540)
81 Facial Neuralgia/ (1121)
82 Facial Pain/ (5019)
83 Glossalgia/ (247)
84 Burning Mouth Syndrome/ (732)
85 Trigeminal Autonomic Cephalalgias/ (105)
86 neuralgia/ or neuralgia, postherpetic/ or piriformis muscle syndrome/ or pudendal neuralgia/ or sciatica/ (12818)
87 neuralgi*.mp. (18296)
88 Post-mastectomy pain.mp. (27)
89 postmastectomy pain syndrome.mp. (24)
90 PMPS.mp. (406)
91 Post-thoracotomy pain.mp. (234)
92 Phantom limb.mp. (1828)
93 agnosia.mp. (2575)
94 Glossodynia.mp. (136)
95 Stomatodynia.mp. (45)
96 (tic adj do?lo?re?ux?).mp. (300)
97 Prosopalgia.mp. (15)
98 meralgia paresthetica.mp. (277)
99 metatarsalgia.mp. (566)
100 (Ramsay adj hunt).mp. (440)
101 odontalgia.mp. (151)
102 sciatica.mp. (5358)
103 (Pain adj2 clinic).ti,ab. (1417)
104 (chronic adj2 pain).ti,ab. (31746)
105 (Neurogen* adj2 pain).ti,ab. (429)
106 low back pain/ (14091)
107 or/80-106 (77534)
108 79 or 107 (176257)
109 (dh or dt or pc or rh or rt or su or th).fs. (5395344)
110 exp Analgesia/ (31987)

111 exp Analgesics/ (433810)
112 analges*.mp. (140770)
113 treat*.mp. (4077132)
114 therap*.mp. (2410630)
115 intervention*.mp. (583724)
116 manag*.mp. (963377)
117 or/109-116 (8422296)
118 108 and 117 (104367)
119 randomized controlled trial.pt. (376906)
120 controlled clinical trial.pt. (88589)
121 randomized.ab. (297403)
122 placebo.ab. (155216)
123 drug therapy.fs. (1709609)
124 randomly.ab. (215113)
125 trial.ab. (308899)
126 groups.ab. (1367352)
127 or/119-126 (3364472)
128 exp animals/ not humans.sh. (3955572)
129 127 not 128 (2886355)
130 118 and 129 (36678)
131 limit 130 to "therapy (maximizes sensitivity)" (30615)
132 limit 131 to "review articles" (6311)
133 131 not 132 (24304)
134 Transcranial Magnetic Stimulation/ (6992)
135 rtms.mp. (2511)
136 magnetics/tu (807)
137 134 or 135 or 136 (8481)
138 pain.mp. (480976)
139 137 and 138 (542)
140 133 or 139 (24765)

Appendix 2: List of chronic neuropathic pain syndromes

- Central neuropathic pain
    - Parkinson disease-related pain
    - Compressive myelopathy from spinal stenosis
    - Post-traumatic spinal cord injury pain
    - Syringomyelia
    - HIV myelopathy
    - Multiple-sclerosis related pain
    - Post-ischemic myelopathy
    - Post-radiation myelopathy
    - Central post-stroke pain
        - Thalamic pain syndrome
        - Dejerine–Roussy syndrome
    - Transverse myelitis

- Peripheral neuropathic pain
    - Alcoholic neuropathy/polyneuropathy
    - Charcot-Marie-Tooth disease
        - Charcot-Marie-Tooth neuropathy
        - Hereditary motor and sensory neuropathy (HMSN)
        - Peroneal muscular atrophy (PMA)
    - Fabry disease (Fabry's disease, Anderson-Fabry disease, angiokeratoma corporis diffusum and alpha-galactosidase A deficiency)
    - Idiopathic sensory neuropathy
    - Nutritional deficiency-related neuropathies
        - Thiamine-deficiency neuropathy/beriberi neuropathy
    - Painful diabetic neuropathy
    - Abdominal migraine
    - Axillary neuropathy
    - Complex regional pain syndrome
        - Reflex sympathetic dystrophy
        - Causalgia
    - Entrapment neuropathies (nerve compression syndromes, compression neuropathy)
        - Anterior interosseous syndrome
        - Carpal tunnel syndrome
        - Cubital tunnel syndrome
        - Guyon's canal syndrome
        - Posterior interosseous neuropathy
        - Pronator teres syndrome
        - Radial neuropathy
        - Struthers' ligament syndrome
        - Wartenberg's Syndrome

- Nerve compression or infiltration by tumour
- Post-mastectomy pain
- Post-thoracotomy pain
- Post-surgical/post-operative neuropathic pain
- Phantom limb pain
- Radiculopathy (cervical, thoracic or lumbosacral)
- Post-traumatic neuralgia
- Meralgia paresthetica (neuropathy of the lateral femoral cutaneous nerve)
- Obturator neruralgia
- Femoral neuralgia
- Sciatic neuralgia
- Morton's neuralgia (interdigital metatarsalgia)
- Piriformis syndrome(technically a variation on sciatic)
- Cauda equina syndrome
- Post mastectomy pain is sometimes referred to (in the IASP taxonomy) as post mastectomypain syndrome
- Post thoracotomy pain syndrome
- Internal mammary artery syndrome (post cardiac surgery Internal Mammary nerve neuralgia)
- Segmental or intercostal neuralgia
- Abdominal cutaneous nerve entrapment syndrome
- Neuralgias of the genitofemoral, ilioinguinal, iliohypogastric, or pudendal nerves
- Facial nerves - neuralgias associated with each and every nerve including the branches of the trigeminal (V1-2-3); 7th nerve (Ramsay Hunt syndrome); glossopharyngeal nerve
- Occipital neuralgias
- Painful opthalmoplegia;
- Odontalgia
- Chronic paroxysmal hemicrania
- Thoracic outlet syndrome
- Acute and chronic inflammatory demyelinating polyradiculoneuropathy
  - Guillain–Barré syndrome
  - Lewis-Sumner syndrome
- Cancer-related neuropathy
  - Chemotherapy-induced peripheral neuropathy
  - Radiotherapy-induced peripheral neuropathy
- HIV-sensory neuropathy
  - HIV-associated distal sensory polyneuropathy (HIV-DSP)
- Postherpetic neuralgia
- Postradiation plexopathy
- Progressive inflammatory neuropathy
- Stomatodynia
  - Glossodynia
  - Burning mouth syndrome
- Toxic exposure-related neuropathies

- Trigeminal neuralgia (Tic douloureux)
  - Prosopalgia
  - Suicide disease
  - Fothergill's disease
- Vasculitic neuropathy
- Wartenberg's migratory sensory neuropathy