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Drug therapy for chronic idiopathic axonal polyneuropathy (Review)

Warendorf J, Vrancken AFJE, van Schaik IN, Hughes RAC, Notermans NC

Warendorf J, Vrancken AFJE, van Schaik IN, Hughes RAC, Notermans NC.
Drug therapy for chronic idiopathic axonal polyneuropathy.
Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD003456.
DOI: 10.1002/14651858.CD003456.pub3.

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[Intervention Review]

Drug therapy for chronic idiopathic axonal polyneuropathy

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Editorial group: Cochrane Neuromuscular Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2017.

Citation: Warendorf J, Vrancken AFJE, van Schaik IN, Hughes RAC, Notermans NC. Drug therapy for chronic idiopathic axonal polyneuropathy. *Cochrane Database of Systematic Reviews* 2017, Issue 6. Art. No.: CD003456. DOI: 10.1002/14651858.CD003456.pub3.

ABSTRACT

Background

Chronic idiopathic axonal polyneuropathy (CIAP) is an insidiously progressive sensory or sensorimotor polyneuropathy that affects elderly people. Although severe disability or handicap does not occur, CIAP reduces quality of life. CIAP is diagnosed in 10% to 25% of people referred for evaluation of polyneuropathy. There is a need to gather and review emerging evidence on treatments, as the number of people affected is likely to increase in ageing populations. This is an update of a review first published in 2004 and previously updated in 2006, 2008, 2011 and 2013.

Objectives

To assess the effects of drug therapy for chronic idiopathic axonal polyneuropathy for reducing disability and ameliorating neurological symptoms and associated impairments, and to assess any adverse effects of treatment.

Search methods

In July 2016, we searched Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews in the Cochrane Library, MEDLINE, Embase, and the Web of Science. We searched two trials registries for ongoing trials. We also handsearched the reference lists of relevant articles, reviews and textbooks identified electronically, and we would have contacted authors and other experts in the field to identify additional studies if this seemed useful.

Selection criteria

We sought all randomised or quasi-randomised (alternate or other systematic treatment allocation) trials that examined the effects of any drug therapy in people with CIAP at least one year after the onset of treatment. People with CIAP had to fulfil the following criteria: age 40 years or older, distal sensory or sensorimotor polyneuropathy, absence of systemic or other neurological disease, chronic clinical course not reaching a nadir in less than two months, exclusion of any recognised cause of the polyneuropathy by medical history taking, clinical or laboratory investigations, and electrophysiological studies in agreement with axonal polyneuropathy, without evidence of demyelinating features. The primary outcome was the proportion of participants with a significant improvement in disability. Secondary outcomes were change in the mean disability score, change in the proportion of participants who make use of walking aids, change in the mean Medical Research Council sum score, degree of pain relief and/or reduction of other positive sensory symptoms, change in the proportion of participants with pain or other positive sensory symptoms, and frequency of adverse effects.

Data collection and analysis

Two review authors independently reviewed the results of the literature search and extracted details of trial methodology and outcome data of all potentially relevant trials.

Main results

We identified 39 studies and assessed them for possible inclusion in the review, but we excluded all of them because of insufficient quality or lack of relevance. We summarised evidence from non-randomised studies in the Discussion.

Authors' conclusions

Even though CIAP has been clearly described and delineated, no adequate randomised or quasi-randomised controlled clinical treatment trials have been performed. In their absence there is no proven efficacious drug therapy.

PLAIN LANGUAGE SUMMARY

Drug therapy for chronic idiopathic axonal polyneuropathy

What is the aim of this review?

The aim of this Cochrane Review was to assess the benefits and harms of drug therapy for chronic idiopathic axonal polyneuropathy (CIAP).

Cochrane Review authors collected and aimed to analyse all relevant studies to answer this question. This is the most recent update of a review first published in 2004.

Key messages

There have not been any randomised trials of drug therapy for CIAP. Future trials will need sensitive outcome measures and long follow-up periods.

What was studied in the review?

CIAP is a frequent disorder in elderly people that can reduce quality of life. Typically, the feet, lower legs and sometimes the hands slowly become numb or weak. The need for evidence-based treatments is increasing as the number of people affected is likely to rise in ageing populations. By definition, the cause of CIAP is unknown.

What are the main results of the review?

We found no trials suitable for review.

How up to date is this review?

The evidence is up to date to July 2016.

BACKGROUND

Chronic idiopathic axonal polyneuropathy (CIAP) typically presents in the sixth decade and is characterised by an insidious onset of predominantly sensory or sensorimotor dysfunction in the legs (Grahmann 1991; McLeod 1984; Notermans 1993; Wolfe 1999). In about 45% of people who have the condition, the polyneuropathy evolves to affect the hands, but involvement of the proximal limbs or cranial nerves does not occur. The distal parts of the limbs are usually symmetrically affected. All those affected have sensory disturbances in the legs, and many also have distal leg weakness. Areflexia is uncommon and usually confined to the ankles or, less frequently, the knees. By definition, electrophysiological studies invariably show an axonal polyneuropathy (Lindh 2005; McLeod 1984; Notermans 1993; Wolfe 1999). The clinical course of CIAP is slowly progressive and often reaches a plateau. Severe disability or handicap does not occur, but quality of life may be reduced (Grahmann 1991; Lindh 2005; Lindh 2011a; McLeod 1984; Notermans 1994; Teunissen 2000a; Vrancken 2002a; Wolfe 1999).

A diagnosis of CIAP can be reached only after exclusion of other causes of axonal polyneuropathy by extensive clinical and laboratory investigations (Farhad 2015; McLeod 1984; Notermans 1993; Rosenberg 2004). CIAP has no characteristic histopathological features. The pathological findings mainly consist of axonal degeneration and regeneration, as well as an increase in endoneurial vessels with basal lamina thickening. Inflammatory changes (increased numbers of inflammatory cells or cellular infiltration) are absent (Chia 1996; Teunissen 2000c; Vrancken 2004a). At the ultrastructural level an increased thickness of endoneurial vessel basal lamina can be found, but this is a non-specific finding (Teunissen 2000c). Consequently, sural nerve biopsy contributes only if another cause of the polyneuropathy is suspected on clinical or laboratory grounds, because histopathological confirmation of an underlying disorder can affect patient management (Chia 1996; Deprez 2000; Gabriel 2000; Logigian 1994).

It is uncertain whether CIAP should be seen as a single entity with a particular (and so far unknown) pathogenesis or whether it represents a heterogeneous group of conditions that share a similar clinical phenotype. Because CIAP typically presents in the elderly and is diagnosed in 10% to 25% of people referred for evaluation of polyneuropathy (Camerlingo 1998; Dyck 1981; Farhad 2015; Grahmann 1991; McLeod 1984; Notermans 1993; Vilming 1987; Visser 2015; Wolfe 1999), the number of people affected and disabled by this condition is expected to increase in the continuously ageing population (Verghese 2001; Visser 2015). Hence, the need for therapy of CIAP is increasing. This is an update of a review first published in 2004.

OBJECTIVES

To assess the effects of drug therapy for chronic idiopathic axonal polyneuropathy for reducing disability and ameliorating neurological symptoms and associated impairments, and to assess any adverse effects of treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We intended to include all randomised or quasi-randomised (alternate or other systematic treatment allocation) studies examining the effects of drug therapy in participants with chronic idiopathic axonal polyneuropathy (CIAP) at least one year after the onset of treatment.

Types of participants

Eligible studies had to include adult participants aged 40 years or older who fulfilled the following criteria for CIAP (Notermans 1993; Vrancken 2002a).

1. Distal sensory or sensory and motor symptoms and signs of the limbs compatible with polyneuropathy.
2. Absence of systemic or neurological disease that could explain the symptoms or signs.
3. Chronic clinical course, not reaching a nadir in less than two months.
4. Exclusion of any recognised cause of the polyneuropathy, such as diabetes mellitus, renal insufficiency, biliary cirrhosis, alcohol abuse, medication use, toxic substance exposure, thyroid disorder, vitamin deficiency, malignancy, polycythaemia, monoclonal protein, systemic autoimmune disease, inflammatory bowel disease, metabolic storage disease, sarcoidosis and amyloidosis, by medical history taking and clinical or laboratory investigations.
5. No indication of hereditary polyneuropathy.
6. Electrophysiological studies in agreement with axonal polyneuropathy without demyelinating features.

Sural nerve biopsy was not mandatory but should have been performed whenever there was any suspicion on clinical or laboratory grounds of an inflammatory or infiltrating disorder (i.e. vasculitis, amyloidosis, or sarcoidosis) or inherited storage disorder (McLeod 1984; Notermans 1993; Vrancken 2004a).

Types of interventions

We would have included any drug therapy versus no therapy, placebo or another drug therapy ('head-to-head' comparison study design). We placed no restrictions on the route of administration.

Types of outcome measures

Primary outcomes

The proportion of participants with a significant improvement in disability as determined by the original authors within or up to one year after the onset of treatment. Where possible, we would have transformed disability data to a modified Rankin scale (Rankin 1957; van Swieten 1988).

- 0 = healthy; no signs or symptoms.
- 1 = no significant disability despite signs and/or symptoms; able to carry out all usual duties.
- 2 = slight disability: unable to carry out usual duties but able to look after own affairs without assistance.

- 3 = moderate disability: requires some help but able to walk without assistance, remains self-supporting.
- 4 = moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance; is only partly self-supporting.
- 5 = severe disability: bedridden and requiring constant care-taking and attention.

If necessary, we would have asked trial authors for original data to enable this transformation. We defined improvement as at least one point decrease on this modified Rankin scale; we considered unchanged or increased scoring on the modified Rankin scale as no improvement.

Secondary outcomes

We considered the following secondary outcome measures (assessed within or up to one year after the onset of treatment and compared to baseline).

1. Change in the mean disability score as determined by the original authors, expressed as standardised mean difference (SMD). Where possible, we would have transformed disability data to the modified Rankin scale as described above.
2. Change in the proportion of participants that makes use of walking aids.
3. Change in the mean Medical Research Council (MRC) sum score (Kleyweg 1991; Notermans 1994; Vrancken 2002a), expressed as SMD.
4. Degree of pain relief, reduction of other positive sensory symptoms or both, as determined by the original authors, expressed as SMD.
5. Change in the proportion of participants with pain or other positive sensory symptoms.
6. Frequency of adverse effects.

If necessary for the meta-analysis, we would have re-scaled the results using the primary or secondary outcome measures from studies with different follow-up periods on the assumption of constant rates of change.

Search methods for identification of studies

Electronic searches

The review authors performed all searches themselves.

We searched:

- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 6 2016) in the Cochrane Library (searched 8 July 2016);
- Cochrane Database of Systematic Reviews (Issue 6, 2016) in the Cochrane Library (searched 8 July 2016);
- MEDLINE (1981 to 8 July 2016);
- Embase (1981 to 6 July 2016);
- Web of Science (1981 to 7 July 2016);
- ClinicalTrials.gov (www.clinicaltrials.gov; searched 7 July 2016); and
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch; searched 7 July 2016).

We used the following keywords as MeSH terms and text words (and their combinations and truncated synonyms) to guide these searches: 'chronic polyneuropathy', 'axonal polyneuropathy', 'cryptogenic polyneuropathy', and 'idiopathic polyneuropathy'. The search began from 1981, when Dyck and colleagues first recognised the clinical entity of idiopathic axonal polyneuropathy (Dyck 1981).

See the appendices for search strategies: Cochrane Register of Studies/Cochrane Central Register of Controlled Trials (CENTRAL; Appendix 1), the Cochrane Library (Appendix 2), MEDLINE Ovid (Appendix 3), Embase (Appendix 4), Web of Science (Appendix 5), ClinicalTrials.gov (Appendix 6) and WHO ICTRP Appendix 7).

Searching other resources

We handsearched the reference lists of relevant published studies, reviews, meta-analyses and textbooks to identify additional studies. We invite readers to suggest studies, particularly in other languages, that we should consider for inclusion when the review is next updated. We would have contacted authors and other experts in the field to identify additional studies if this seemed useful.

Data collection and analysis

Selection of studies

Two authors (AV and IS or JW) independently reviewed the titles and abstracts from literature searches to identify potentially relevant trials for full review. From the full texts, we would have selected trials that met the selection criteria and graded their risk of bias. Review authors were not blinded to trial author or source institution. We would have resolved disagreement by consensus with third party adjudication if necessary.

Data extraction and management

Two review authors (AV and IS or JW) would have independently extracted data onto specially designed, pre-piloted collection forms. We would have obtained missing data from the trial authors whenever possible. We would have resolved disagreements by consultation with a third author until we reached consensus.

Assessment of risk of bias in included studies

We would have assessed concealment of treatment allocation, randomisation, incomplete outcome data (and intention-to-treat analysis), selective outcome reporting, participant and personnel blinding, observer blinding, and other sources of bias. We would have scored each item according to the *Cochrane Handbook for Systematic Reviews of Interventions* as conferring a low, high or unclear (uncertain) risk of bias (Higgins 2011). Two authors (AV and IS or JW) would have graded the risk of bias independently. In case of disagreement, we would have consulted another review author for resolution by consensus.

Measures of treatment effect

We would have used Review Manager 5 (RevMan 5) software to carry out calculations (RevMan 2014). We would have calculated risk ratios (RRs) from dichotomised proportional data for each study. We would have calculated the pooled risk ratio estimate to assess the overall efficacy of the intervention in comparable studies.

We would have calculated mean differences (MD) from the mean changes in disability scores and MRC scores for each study if studies

used the same measure. If studies used different measurement tools for the same continuous outcome we would have calculated the standardised mean difference (SMD) to combine results. We planned to derive standard deviations for each study by calculation or extraction from the available data. If necessary we would have asked trial authors for the original data. For all analyses, we would have determined 95% confidence intervals.

Assessment of heterogeneity

We would have quantified heterogeneity of data by I^2 analysis (Higgins 2011). If this analysis had shown heterogeneity to be low (I^2 smaller than or equal to 25%), we would have used the Mantel-Haenszel fixed-effect model. Otherwise, we would have carried out sensitivity analyses first to explore the plausible cause of the heterogeneity of data.

Data synthesis

We planned to use a fixed-effect meta-analysis as noted above. If heterogeneity were not due to differences between identifiable and separable subgroups of studies, we would have employed the random-effects model of DerSimonian and Laird (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We would have performed subgroup analyses to explore possible differences in treatment efficacy between participants younger than 65 years and 65 years and older, and between participants with a nadir of neurological deficits within or after 12 months from the onset of symptoms and signs (Vrancken 2002a; Vrancken 2004a).

Sensitivity analysis

We would have performed a sensitivity analysis on the basis of risk of bias, according to the presence or absence of allocation concealment and other bias domains. We would have also used sensitivity analyses to explore the origin of unexplained heterogeneity within analyses.

'Summary of findings' table

If RCTs are available for inclusion in future updates, we will create a 'Summary of findings' table using the outcomes listed under Types of outcome measures . We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence (studies that contribute data for the prespecified outcomes). We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software. Two or more authors will grade the evidence independently and resolve differences by consensus. We will justify all decisions to downgrade or upgrade the quality of studies using footnotes, and we will make comments to aid readers' understanding of the review where necessary.

RESULTS

Description of studies

For this updated review the number of studies found by the new, current search strategies were: MEDLINE, 564 (197 new); Embase, 87 (49 new); Cochrane Reviews in the *Cochrane Library,* 143 (61 new); CENTRAL, 188 (117 new); and Web of Science, 158 (57 new). We identified and assessed 42 studies (12 new) for possible inclusion in the review. Twenty-two studies did not show separate data for participants with idiopathic (poly)neuropathy (Attal 2016; De Grandis 1995; Demant 2014; Gilron 2011; Hewitt 2011; Holbech 2011; Husstedt 1993; Jensen 2012; Kishore-Kumar 1989; Li 2010; Low 1995; Morley 2003; Otto 2008; Raber 2015; Sindrup 1999a; Sindrup 1999b; Sindrup 2001; Sindrup 2003; Sindrup 2012; Vrethem 1997; Wallace 2000; Wilsey 2013); 17 studies included participants with neuropathic pain and painful (poly)neuropathy of various, unspecified or unclear origin (Frank 2008; Galer 2000; Haanpaa 2016; Ho 2008; Huge 2010; Langohr 1982; Maier 2002; Meier 2003; Nurmikko 2007; Onofrj 1995; Otto 2004; Pedersen 2014; Rauck 2006; Rowbotham 2003; Semenchuk 2001; Serpell 2014; Wallace 2002); 3 studies did not include useful outcome measures (Bradley 1988; De Grandis 1995; Husstedt 1993); and 2 studies concerned participants with painful idiopathic small fiber predominant neuropathy (Ho 2009; Windebank 2004). In none of the assessed studies did the participants with idiopathic (poly)neuropathy fulfil our criteria for CIAP. Thus, we excluded all studies for this review update. We have provided details of all the excluded studies in Characteristics of excluded studies.

At this update, we identified two potentially eligible ongoing studies: one randomised study of the safety and effectiveness of nortriptyline, duloxetine, pregabalin and mexiletine for treating cryptogenic sensory polyneuropathy (NCT02260388), and another randomised, double-blind, controlled study of lidocaine for neuropathic pain (NCT02597257). See Characteristics of ongoing studies.

Risk of bias in included studies

No studies were of sufficient quality to be included.

Effects of interventions

No included studies.

DISCUSSION

Even though chronic idiopathic axonal polyneuropathy (CIAP) has been clearly described and delineated, no adequate randomised or quasi-randomised controlled clinical trials for its treatment have been published. Perhaps the mild and non-severely disabling clinical course has until now obviated the need for such studies, but since the neurological symptoms and signs interfere with physical functioning and activities of daily living, and consequently lead to a reduced quality of life, it is justifiable to seek treatments.

In the only open study that included five participants with a more progressive course of idiopathic axonal polyneuropathy (i.e. nadir within one year of disease onset, and no evidence of vasculitis or inflammation in a sural nerve biopsy), investigators observed no clear benefit for treatment with oral prednisone or intravenous immunoglobulin (Vrancken 2004a). Thus, at present there are no promising observational studies to guide the choice of treatment for CIAP.

In the absence of a proper understanding of the pathogenesis of CIAP, it is not possible to propose specific treatments for study. Given that this is an axonal peripheral neuropathy, it may appear relatively unlikely that any current therapeutic approach could cause improvement with respect to the primary outcome measure, and that at best stabilisation or slowing in deterioration could be achieved in terms of the secondary outcome measures.

There may be an association between impaired glucose tolerance and idiopathic painful sensory neuropathy (Rajabally 2011a), but for CIAP this is very uncertain (Nebuchennykh 2008; Visser 2013). Moreover, in follow-up studies participants with CIAP did not develop diabetes (Jann 2001; Notermans 1994; Vrancken 2002a). Chronic obstructive pulmonary disease, subtle cobalamin deficiency, use of statins, vitamin B6 exposure, cardiovascular disease or associated risk factors such as hypertriglyceridaemia, hypertension, obesity, or the metabolic syndrome, and exposure to environmental or occupational risk factors have been implicated in predisposing to polyneuropathy without a cause, that is idiopathic or cryptogenic (axonal) polyneuropathy (Baldereschi 2013; Bays 2006; Hughes 2004; Jann 1998; Lindh 2011b; Persson 2013; Poza 1997; Rajabally 2011b; Saperstein 2003; Singer 2012; Smith 2008; Teunissen 2002; Tierney 2013; Tondel 2006; Visser 2013; Visser 2014). The microvascular changes in nerve biopsies of people with CIAP further support the hypothesis that chronic ischaemia or hypoxaemia could play a role in the pathogenesis of CIAP (Teunissen 2000b; Teunissen 2000c). Thus, drug treatment or lifestyle changes similar to those recommended for (risk factors of) cardiovascular disease or diabetes are worth considering (Bhalla 2014; Cameron 2001; Eliasson 2003; Forrest 1997; Hernandez-Ojeda 2014; Malik 2000; Smith 2006). Alpha-lipoic acid has been shown to improve symptoms in diabetic polyneuropathy (Ziegler 2011). Vitamin B treatment for polyneuropathy is the subject of another Cochrane Review (Ang 2008).

Alternative approaches would be to test neurotrophic factors or strategies that improve the neuroprotective and neuroregenerative properties of Schwann cells (Fressinaud 2003; Lehmann 2010; Leinninger 2004; Pradat 2003; Sah 2003); another would be to test agents that have been shown to be effective in neurodegenerative conditions, for example riluzole, which increases survival time in motor neuron disease (Miller 2012). Neuroimmunophilin ligands such as tacrolimus derivatives without immunosuppressive properties, Rho kinase inhibitors, or neuroactive steroids also have neuroprotective and neuroregenerative activity (Höke 2005; Müller 2005; Roglio 2008). During the processes of Wallerian degeneration, nitric oxide plays a central role and contributes to the development of neuropathic pain (Zochodne 2005). Thus, hypothetically, agents that prevent nitric oxide formation such as nitric oxide synthase inhibitors may form treatment options in the future, but no studies to date have investigated their possible clinical usefulness.

Without drug therapies that prevent progression, clinicians and patients must resort to symptomatic treatments. Pain can be a prominent feature in people with CIAP (Erdmann 2010). Treatment of neuropathic pain is the subject of various systematic reviews and meta-analyses, including Cochrane Reviews (Challapalli 2005; Chaparro 2012; Derry 2013; Derry 2015; Duehmke 2006; Finnerup 2015; McNicol 2013; Moore 2015a; Moore 2015b; Moore 2015c; Thompson 2015; Wiffen 2013; Wiffen 2014; Wiffen 2015; Wrzosek 2015), and evidence-based guidelines including the cost-effectiveness of therapy have been proposed (Attal 2010; Attal 2015; Cepeda 2006; Smith 2013). With increased understanding of the role of ion channels in neuropathic pain, new therapeutic agents aimed at these ion channels are emerging and could be worth considering (Cohen 2014; Gilron 2014; Markman 2006).

Some people have foot drop, for which ankle-foot orthoses and other rehabilitative measures can be useful. The effect of exercise in peripheral neuropathy is the subject of a recent review and a Cochrane Review (Streckmann 2014; White 2004), and another Cochrane Review has also evaluated interventions for fatigue (White 2014). Effective methods for offering advice about foot care would also be worth considering since analgesia of the feet is a common feature.

The slow progression and mild disability produced by CIAP make it difficult to design adequate clinical trials. We recommend selecting a sensitive disability outcome measure as being more directly relevant to people's needs than an electrophysiological, pathological or impairment measure. Even though we preferred the modified Rankin scale for this review, a scale with more steps that is designed for measuring disability in peripheral neuropathy might be superior. Investigators should consider disability scores designed to measure upper- and lower-limb disability that have been validated for assessing change and reflect people's judgment in inflammatory neuropathies (Graham 2006a; Merkies 2006). Alternatively, since most people with CIAP experience difficulty walking, a scale that has been validated for evaluating walking disability in peripheral neuropathy would be useful (Graham 2006b). Although the time frame for measurements of outcomes cannot be known with certainty, clinical follow-up in people with CIAP demonstrated stabilisation within the first five years after disease onset (Dyck 1981; McLeod 1984; Grahmann 1991; Notermans 1994; Jann 2001; Vrancken 2002a). Because of its slow progression, change in outcome measures will need to be assessed after long time intervals, for example after at least one and preferably two or three years. Since the disability produced by CIAP is mild and therapy is likely to be needed over a long period of time, it will be particularly important to identify inexpensive treatments that are not hampered by serious side effects.

AUTHORS' CONCLUSIONS

Implications for practice

There are no randomised trials on which to base drug treatment for chronic idiopathic axonal polyneuropathy (CIAP).

Implications for research

More research is needed on drug treatment for CIAP. Randomised trials will need to be long term and use sensitive outcome measures.

ACKNOWLEDGEMENTS

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

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Attal 2016	Neuropathic pain of various origins, including idiopathic sensory neuropathy No separate analyses for idiopathic sensory neuropathy Idiopathic sensory neuropathy not well defined (i.e. not defined as CIAP)
Bradley 1988	No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP) No useful outcome measures
De Grandis 1995	No separate analyses for idiopathic neuropathy Idiopathic neuropathy not well defined (i.e. not defined as CIAP) No useful outcome measures
Demant 2014	Peripheral neuropathic pain of various origins, including idiopathic polyneuropathy No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
Frank 2008	Neuropathic pain of various origins, including unspecified neuropathy (i.e. not defined as CIAP)
Galer 2000	Diabetic and non-diabetic polyneuropathy of various unspecified origins
Gilron 2011	Hereditary/idiopathic peripheral neuropathy taken as one group No separate analyses for idiopathic peripheral neuropathy Idiopathic peripheral neuropathy not well defined (i.e. not defined as CIAP)
Haanpaa 2016	Neuropathic pain of various origins, including non-diabetic painful peripheral polyneuropathy, (i.e. not defined as CIAP)
Hewitt 2011	Neuropathic pain of various origins, including idiopathic sensory neuropathy No separate analyses for idiopathic sensory neuropathy Idiopathic sensory neuropathy not well defined (i.e. not defined as CIAP)
Ho 2008	Neuropathic pain of various origins, including unspecified peripheral neuropathy (i.e. not defined as CIAP)
Ho 2009	Idiopathic small fiber neuropathy (i.e. not defined as CIAP)
Holbech 2011	Painful polyneuropathy of various origins, including idiopathic polyneuropathy No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
Holbech 2015	Painful polyneuropathy of various origins, including idiopathic polyneuropathy No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
Huge 2010	Neuropathic pain of various origins, including unspecified painful polyneuropathy (i.e. not defined as CIAP)

Study	Reason for exclusion
Husstedt 1993	No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP) No useful outcome measures
Jensen 2012	Neuropathic pain of various origins, including idiopathic sensory neuropathy No separate analyses for idiopathic sensory neuropathy Idiopathic sensory neuropathy not well defined (i.e. not defined as CIAP)
Kishore-Kumar 1989	No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
Langohr 1982	Painful polyneuropathies of various origins (i.e. not defined as CIAP)
Li 2010	No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
Low 1995	No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
Maier 2002	Neuropathic pain of various origins, including unspecified painful polyneuropathy (i.e. not defined as CIAP).
Meier 2003	Neuropathic pain of various or unclear origins, including unspecified neuropathy (i.e. not defined as CIAP)
Morley 2003	Neuropathic pain of various origins, including idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
NCT00156689	Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP, inclusion criteria: normal conduction studies)
Nurmikko 2007	Neuropathic pain of various or unclear origins, including unspecified peripheral neuropathy (i.e. not defined as CIAP)
Onofrj 1995	Cervical and lumbosacral painful syndromes of various origins
Otto 2004	Painful diabetic and non-diabetic polyneuropathy of various unspecified origins
Otto 2008	No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
Pedersen 2014	Chronic non-malignant pain of various origins, including 1 patient with unspecified painful polyneuropathy (i.e. not defined as CIAP)
Raber 2015	No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
Rauck 2006	Pain of various types of unspecified origins, including peripheral neuropathic pain
Rowbotham 2003	Pain from the central nervous system or peripheral nervous system, including peripheral neuropathy of unspecified origins (i.e. not defined as CIAP)
Semenchuk 2001	Neuropathic pain of various origins, including peripheral neuropathy (i.e. not defined as CIAP)
Serpell 2014	Peripheral neuropathic pain of various origins, including unspecified peripheral neuropathy (i.e. not defined as CIAP)

Study	Reason for exclusion
Sindrup 1999a	No separate analyses for idiopathic polyneuropathy. Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP).
Sindrup 1999b	No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
Sindrup 2001	No separate analyses for idiopathic polyneuropathy. Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP).
Sindrup 2003	No separate analyses for idiopathic polyneuropathy. Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP).
Sindrup 2012	Painful polyneuropathy of various origins, including idiopathic polyneuropathy No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
Vrethem 1997	No separate analyses for idiopathic polyneuropathy Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP)
Wallace 2000	No separate analyses for idiopathic peripheral neuropathy Idiopathic peripheral neuropathy not well defined (i.e. not defined as CIAP)
Wallace 2002	Neuropathic pain of various origins, including unspecified peripheral neuropathy (i.e. not defined as CIAP)
Wilsey 2013	Neuropathic pain of various origins, including idiopathic sensory neuropathy No separate analyses for idiopathic sensory neuropathy Idiopathic sensory neuropathy not well defined (i.e. not defined as CIAP)
Windebank 2004	Painful idiopathic distal symmetric neuropathy Unclear if alcohol abuse, hypothyroidism, vitamin deficiency, pyridoxine (vitamin B6) intoxication, monoclonal gammopathy were sufficiently excluded Unclear if electrophysiological criteria for CIAP were met

CIAP: chronic idiopathic axonal polyneuropathy.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02260388

Trial name or title	Patient assisted intervention for neuropathy: comparison of treatment in real life situations (PAIN-CONTRoLS)
Methods	Testing of 4 drugs for participants with cryptogenic sensory polyneuropathy
Participants	Diagnosis of CSPN, Likert pain score greater than or equal to 4, aged 30 years or older
Interventions	Nortriyptilne 25 mg daily for 1 week at bedtime, then 50 mg daily for 1 week, ten 75 mg daily for the remainder of the study Duloxetine 20 mg daily for 1 week, then 40 mg daily for 1 week, then 60 mg for the remainder of the study Pregabalin 100 mg daily for 1 week, then 100 mg 2 times per day for 1 week, then 100 mg 3 times per day for the remainder of the study

NCT02260388 *(Continued)*

	Mexiletine 200 mg daily for 1 week, then 200 mg 2 times per day for 1 week, then 200 mg 3 times per day for the remainder of the study
Outcomes	Change in patient-reported pain, percentage discontinuing treatment, change in general health and wellbeing using the Short Form 12 Health Survey questionnaire, pain interference, change in fatigue and quality of sleep (NIH Sleep Disturbance Scale) Time frame: 12 weeks
Starting date	2014
Contact information	Maureen Walsh: email mwalsh@kumc.edu
Notes	Recruiting

NCT02597257

Trial name or title	Efficacy and safety of lidocaine infusion treatment in management of neuropathic pain
Methods	Randomized, double-blind, controlled study
Participants	Post-herpetic neuralgia, diabetic polyneuropathy and peripheral polyneuropathy
Interventions	Lidocaine continuous infusion 3 mg/kg or normal saline
Outcomes	11-point numeric rating scale (pain) after 1 week At the end of the intervention and 4 weeks later: Brief Pain Inventory Short Form Short Form McGill Pain Questionnaire Patient Global Impression of Change Adverse events
Starting date	2015
Contact information	Yong Chul Kim, Seoul National University Hospital pain@snu.ac.kr
Notes	Recruiting

APPENDICES

Appendix 1. Cochrane Register of Studies Online/Cochrane Central Register of Controlled Trials (CENTRAL; crso.cochrane.org) search strategy

Search run on Thu Jul 7 2016

#1 (chronic idiopathic axonal polyneuropathy):TI,AB,KY 1

#2 ciap:TI,AB,KY 3

#3 (chronic NEAR3 (axonal polyneuropathy OR axonal neuropathy)):TI,AB,KY 2

#4 ((axonal OR idiopathic OR cryptogenic) NEAR (polyneuropathy OR neuropathy)):TI,AB,KY 44

#5 #1 OR #2 OR #3 OR #4 46

#6 (polyneuropathy OR "peripheral neuropathy") 2355

#7 "painful neuropathy" OR "painful polyneuropathy" OR "neuropathic pain" 1170

#8 #6 AND #7 187

#9 #5 OR #8 230

#10 (random* OR placebo* OR crossover OR cross-over) NEAR (trial OR study) 557938

#11 #9 AND #10 188

Appendix 2. The Cochrane Library (cochranelibrary.com) (Cochrane reviews, Cochrane Central Register of Controlled Trials) search strategy

Date Run:08/07/16 10:41:31.253
Description:

IDSearchHits
#1chronic idiopathic axonal polyneuropathy 10
#2ciap 8
#3chronic near/3 (axonal polyneuropathy or axonal neuropathy) 8
#4(axonal or idiopathic or cryptogenic) near (polyneuropathy or neuropathy) 77
#5#1 or #2 or #3 or #4 85
#6(polyneuropathy or "peripheral neuropathy") 2805
#7"painful neuropathy" or "painful polyneuropathy" or "neuropathic pain" 1490
#8#6 and #7 262
#9#5 or #8 334
#10(random* or placebo* or crossover or cross over) near (trial or study) 597732
#11#9 and #10 Publication Year from 1981 to 2016, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Trials and Cochrane Groups, with Neuromuscular Disease Group

Appendix 3. MEDLINE (ovidsp.tx.ovid.com) search strategy

Date of search: 08-07-2016

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

Search Strategy:

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1 randomized controlled trial.mp. (438735)

2 controlled clinical trial.mp. (101181)

3 (single-blind method or double-blind method or cross-over studies or random allocation or control groups or clinical trial or multicenter study or meta-analysis).mp. (1046661)

4 2 or 3 (1046661)

5 (trial or placebo or dummy or sham or random$).tw. (1163656)

6 4 and 5 (487843)

7 1 or 6 (655866)

8 (drug therapy or "therapeutic use").fs. (2537844)

9 7 and 8 (282078)

10 exp animals/ not humans.sh. (4276104)

11 9 not 10 (272971)

12 chronic idiopathic axonal polyneuropath$.tw. (49)

13 (ciap and axonal).tw. (32)

14 (chronic adj10 axonal neuropath$).tw. (84)

15 (chronic adj10 axonal polyneuropath$).tw. (85)

16 ((axonal or cryptogenic or idiopathic) adj10 neuropath$).tw. (3642)

17 ((axonal or cryptogenic or idiopathic) adj10 polyneuropath$).tw. (1046)

18 12 or 13 or 14 or 15 or 16 or 17 (4349)

19 exp polyneuropathies/ or polyneuropath$.tw. (31703)

20 peripheral neuropath$.tw. (16237)

21 19 or 20 (45651)

22 (painful or neuropathic pain).tw. (60576)

23 21 and 22 (2545)

24 (idiopathic or cryptogenic).mp. (107469)

25 23 and 24 (62)

26 18 or 25 (4363)

27 (11 and 22) not painful.tw. (566)

28 11 and 26 (26)

29 27 or 28 (589)

30 limit 29 to yr="1981-Current" (589)

31 remove duplicates from 30 (564)

****

Appendix 4. Embase (embase.com) search strategy

Embase Session Results (6 Jul 2016)

No.	Query	Results
#27	#11 AND #25 AND [1981-2016]/py	87
#26	#11 AND #25	87
#25	#20 OR #23 OR #24	6880
#24	#20 AND #22	321
#23	#18 AND #21	81
#22	'neuropathic pain'	29230
#21	painful NEXT/10 (neuropath* OR polyneuropath*)	3315

(Continued)

#20	#16 OR #19	6867
#19	#17 AND #18	1641
#18	cryptogenic OR idiopathic	154739
#17	polyneuropathy OR 'peripheral neuropathy' OR 'sensorimotor neuropathy' OR 'sensory neuropathy'	78908
#16	#12 OR #13 OR #14 OR #15	5876
#15	(axonal OR idiopathic OR cryptogenic) NEXT/10 (neuropath* OR polyneuropath*)	5876
#14	chronic NEXT/10 ('axonal neuropathy' OR 'axonal neuropathies' OR 'axonal polyneuropathy' OR 'axonal polyneuropathies')	204
#13	ciap AND axonal	46
#12	'chronic idiopathic axonal' NEXT/1 (neuropath* OR polyneuropath*)	70
#11	#9 NOT #10	324394
#10	'nonhuman'/exp NOT 'human'/exp	3742697
#9	#5 AND #8	326002
#8	#1 OR #7	711796
#7	#4 AND #6	501083
#6	#2 OR #3	659625
#5	'drug therapy':de,lnk,cl	3653522
#4	trial OR placebo OR dummy OR sham OR random*	2299323
#3	'crossover procedure' OR 'comparative effectiveness' OR 'factorial design' OR 'single blind procedure' OR 'double blind procedure' OR 'triple blind procedure' OR 'study design'	384332
#2	'controlled clinical trial'	377972
#1	'randomized controlled trial'	512011

Appendix 5. Web of Science (apps.webofknowledge.com) search strategy

Date of search: 07-07-2016

Search History:

Set	Results

(Continued)

# 18	**158**	#17 AND #7 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 17	2,532	#16 OR #12 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 16	188	#15 AND #10 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 15	6,600	#14 AND #13 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 14	82,478	TS=(neuropathy OR polyneuropathy) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 13	61,090	TS=painful OR TS=(neuropathic pain) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 12	2,532	#11 OR #8 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 11	2,532	#10 AND #9 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 10	115,146	TS=(idiopathic) OR TS=(cryptogenic) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 9	133,612	TS=(neuropath*) OR TS=(polyneuropathy) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*

(Continued)

# 8	2,532	TS=(idiopathic neuropath*) OR TS=(idiopathic polyneuropathy) OR TS=(cryptogenic neuropath*) OR TS=(cryptogenic polyneuropathy) OR TS=(chronic idiopathic axonal polyneuropathy) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 7	981,085	#6 AND #4 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 6	3,254,651	#5 OR #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 5	2,800,972	#3 AND #2 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 4	1,378,127	TS=(random*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 3	16,086,029	TS=(trial) OR TS=(study) OR TS=(treatment) OR TS=(treated) OR TS=(therap*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 2	4,955,372	TS=(placebo) OR TS=(blind*) OR TS=(control*) OR TS=(crossover) OR TS=(cross-over) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*
# 1	977,983	TS=(random* trial) OR TS=(random* study) OR TS=(random* treatment) OR TS=(randomi* therap*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*

Appendix 6. ClinicalTrials.gov search strategy

Date of search: 07-07-2016

Search Terms: polyneuropathy

Targeted Search Conditions: polyneuropathy

Search syntax: polyneuropathy AND polyneuropathy [DISEASE]

Result: 251 studies found

Appendix 7. WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/AdvSearch.aspx) search strategy

Date of search: 07-07-2016

Polyneuropathy in the Title AND Polyneuropathy in the Condition

Recruitment status is: All

Date of registration is up until: 07/07/2016

Result: 175 records for 104 trials found

WHAT'S NEW

Date	Event	Description
7 July 2016	New search has been performed	Minor edits. Conclusions unchanged.
11 April 2016	New citation required but conclusions have not changed	Searches incorporated. No new trials; 2 ongoing trials. Discussion updated with new non-randomised studies.

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 2, 2004

Date	Event	Description
4 March 2013	Amended	Added Published notes concerning the next scheduled update of this review.
15 February 2011	New search has been performed	Searches updated: the Cochrane Neuromuscular Disease Group Trials Register (April 2011), CENTRAL to Issue 1, 2011, MEDLINE (January 1981 to February 2011), EMBASE (January 1981 to February 2011), ISI (January 1981 to February 2011). No relevant trials were found. Discussion edited and references updated. Risk of bias section in methods revised.
1 July 2006	New search has been performed	We updated the searches of the NMD Group Trials Register (April 2006), MEDLINE (January 1981 to May 2006), EMBASE (January 1981 to May 2006), ISI (January 1988 to May 2006) and ACP Journal Club's Best Evidence (January 1991 to May 2006). No randomised controlled trials were found. New non-randomised studies were added to the Discussion section of the review.
10 January 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Alexander Vrancken extracted the data and wrote the first draft. Ivo van Schaik and Janna Warendorf also extracted data. All authors contributed to subsequent drafts and agreed the final version.

DECLARATIONS OF INTEREST

Janna Warendorf: none known.

Alexander Vranken: none known.

Ivo van Schaik: received departmental honoraria for serving on scientific advisory boards for CSL-Behring, Baxter and UCB, and a speaker's fee from Kedrion and CSL-Behring. He chairs a steering committee for CSL-Behring.

Richard Hughes: none known.

Nicolette Notermans: none known.

SOURCES OF SUPPORT

Internal sources

- The Rudolf Magnus Institute for Neuroscience, University Medical Center Utrecht, Department of Neurology and Neuromuscular Diseases, Netherlands.
- Academic Medical Center, University of Amsterdam, Department of Neurology, Netherlands.
- King's College London School of Medicine, London, UK.
- Cochrane Neuromuscular Disease Group, MRC Centre for Neuromuscular Disease, National Hospital for Neurology and Neurosurgery, London, UK.
- Academic Medical Center, University of Amsterdam, Department of Biostatistics and Clinical Epidemiology, Netherlands.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We revised the risk of bias methods section according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We included methods for creating 'Summary of findings' tables.

We no longer search the American College of Physicians (ACP) Journal Club, which was listed in the protocol (Vrancken 2002b), as the search has not yielded useful results. We included searches of clinical trials registries.

NOTES

In 2016 the review authors incorporated new searches. As the review has no included trials, the review underwent minor revisions without comprehensive application of current standards. New evidence on this topic is slow to emerge. The next update is planned for 2020, which is four years after the last search rather than the usual two years. If new trials are published in the interim we will schedule an earlier update.

INDEX TERMS

Medical Subject Headings (MeSH)

Axons; Chronic Disease; Gait Ataxia [drug therapy] [etiology]; Leg [*innervation]; Polyneuropathies [*drug therapy]

MeSH check words

Aged; Humans