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Drug therapy for chronic idiopathic axonal polyneuropathy (Review)

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

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Drug therapy for chronic idiopathic axonal polyneuropathy.
Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD003456.
DOI: 10.1002/14651858.CD003456.pub2.

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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: Edited (no change to conclusions), published in Issue 4, 2013.
Review content assessed as up-to-date: 15 February 2011.

Citation: Vrancken AFJE, van Schaik IN, Hughes RAC, Notermans NC. Drug therapy for chronic idiopathic axonal polyneuropathy. *Cochrane Database of Systematic Reviews* 2004, Issue 2. Art. No.: CD003456. DOI: 10.1002/14651858.CD003456.pub2.

ABSTRACT

Background

Chronic idiopathic axonal polyneuropathy is an insidiously progressive sensory or sensorimotor polyneuropathy that affects elderly people. Although severe disability or handicap does not occur, it reduces quality of life. This is an updated review.

Objectives

To assess whether drug therapy for chronic idiopathic axonal polyneuropathy reduces disability, ameliorates neurological symptoms and associated impairments, and whether treatment is safe.

Search methods

We searched the Cochrane Neuromuscular Disease Group Specialized Register (3 April 2011), The Cochrane Central Register of Controlled Trials CENTRAL (Issue 1, 2011) in *The Cochrane Library*, MEDLINE (January 1981 to 15 February 2011), EMBASE (January 1981 to 15 February 2011), and ISI Web of Knowledge (1981 to February 2011). We also handsearched the reference lists of relevant articles, reviews and textbooks identified electronically, and authors and other experts in the field were to be contacted to identify additional studies if this seemed useful.

Selection criteria

We sought all randomised or quasi-randomised (alternate or other systematic treatment allocation), unconfounded trials that examined the effects of any drug therapy in patients with chronic idiopathic axonal polyneuropathy at least one year after the onset of treatment. Patients with chronic idiopathic axonal polyneuropathy 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, electrophysiological studies in agreement with axonal polyneuropathy without evidence of demyelinating features. The primary outcome was the proportion of patients with a significant improvement in disability. Secondary outcomes were change in the mean disability score, change in the proportion of patients 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 patients with pain or other positive sensory symptoms, and frequency of adverse effects.

Data collection and analysis

Two authors independently reviewed and extracted details of trial methodology and outcome data of all potentially relevant trials.

Main results

We identified 30 studies and assessed them for possible inclusion in the review, but all were excluded because of insufficient quality or lack of relevance.

Authors' conclusions

Even though chronic idiopathic axonal polyneuropathy 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

Chronic idiopathic axonal polyneuropathy is a frequent disorder in elderly persons that is characterised by very slowly progressive numbness or weakness of the feet and lower legs, and sometimes the hands. By definition, the cause is not known. No randomised trials of drug treatment for chronic idiopathic axonal polyneuropathy have been conducted. Trials will need sensitive outcome measures and long follow-up periods. This is an updated review.

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 (McLeod 1984; Grahmann 1991; Notermans 1993; Wolfe 1999). In about 45% of patients 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 patients 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; Notermans 1994; 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 (Lindh 2005; McLeod 1984; Grahmann 1991; Notermans 1993; Notermans 1994; Wolfe 1999; Teunissen 2000a).

The diagnosis of CIAP is made after exclusion of other causes of axonal polyneuropathy by extensive clinical and laboratory investigations (McLeod 1984; Notermans 1993). There are no characteristic histopathological features of CIAP. 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; Bosboom 2000; Teunissen 2000c). 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 (Argov 1989; Neundörfer 1990; Oh 1990; Rappaport 1993; Logigian 1994; Chia 1996; Deprez 2000; Gabriel 2000).

It is uncertain whether CIAP should be seen as a single entity with a particular 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 patients referred for evaluation of polyneuropathy (Dyck 1981; McLeod 1984; Vilming 1987; Grahmann 1991; Notermans 1993; Camerlingo 1998; Wolfe 1999), the number of people affected and disabled by this condition is expected to increase in the continuously ageing population. Hence, there is an increasing need for therapy of CIAP.

OBJECTIVES

The objective was to review systematically the evidence from randomised controlled trials concerning the effects of drug treatment on CIAP.

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 patients with CIAP at least one year after the onset of treatment.

Types of participants

Eligible studies had to include adult patients of at least 40 years or older who fulfilled the following criteria for CIAP:

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 (Dyck 1981; McLeod 1984; Notermans 1993).

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, sarcoidosis) or inherited storage disorder (McLeod 1984; Notermans 1993).

Types of interventions

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

Types of outcome measures

Primary outcomes

The proportion of patients 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, disability data were to be transformed 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, authors were to be asked for the original data to enable this transformation. Improvement was defined as at least one point decrease on this modified Rankin scale. Unchanged or increased scoring on the modified Rankin scale was considered as no improvement.

Secondary outcomes

Secondary outcome measures (assessed within or up to one year after the onset of treatment and compared to baseline):

1. the change in the mean disability score as determined by the original authors expressed as standardised mean difference (SMD). Where possible, disability data were to be transformed to the modified Rankin scale as described above;
2. the change in the proportion of patients that make use of walking aids;
3. the change in the mean MRC sum score (Kleyweg 1991; Dyck 1991; Dyck 1992) expressed as SMD;
4. the degree of pain relief and/or reduction of other positive sensory symptoms as determined by the original authors expressed as SMD;
5. the change in the proportion of patients with pain or other positive sensory symptoms;
6. the frequency of adverse effects.

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

Search methods for identification of studies

Electronic searches

We searched The Cochrane Neuromuscular Disease Group Specialized Register (3 April 2011), The Cochrane Central Register of Controlled Trials CENTRAL (Issue 1, 2011) in *The Cochrane Library*, MEDLINE (January 1981 to 15 February 2011), EMBASE (January 1981 to 15 February 2011) and ISI Web of Knowledge (January 1981 to 15 February 2011). The authors themselves carried out all searches other than the Cochrane Neuromuscular Disease Group Specialized Register search. The following keywords as MeSH terms and textwords (and their combinations and truncated synonyms) were used to guide these searches: 'chronic polyneuropathy', 'axonal polyneuropathy', 'cryptogenic polyneuropathy', and 'idiopathic polyneuropathy'. The search began from 1981, because the clinical entity of idiopathic axonal polyneuropathy was then first recognised by Dyck and colleagues (Dyck 1981). The reference lists of relevant published studies, reviews, meta-analyses, and textbooks were handsearched to identify additional studies. Readers are invited to suggest studies, particularly in other languages, which should be considered for inclusion when the review is updated.

The search strategies are outlined in Appendix 1, Appendix 2, Appendix 3 and Appendix 4.

Data collection and analysis

Selection of studies

Two authors (AV and IS) independently reviewed the titles and abstracts from literature searches to identify potentially relevant trials for full review. From the full texts, trials that met the selection criteria would have been selected for inclusion and grading of their methodological quality. Authors were not blinded to author and source institution. Disagreement was to be resolved by consensus with third party adjudication if necessary.

Data extraction and management

Two independent authors (AV and IS) would have extracted data onto specially designed collection forms that had been tested prior to use. Missing data would have been obtained from the authors whenever possible. Disagreements were to be resolved by consultation with a third author until consensus was reached.

Assessment of risk of bias in included studies

We would have assessed allocation concealment of treatment, randomisation, intention-to-treat analysis, confounding, patient blinding, observer blinding, explicit diagnostic inclusion and exclusion criteria and explicit outcome criteria. Each item was to be scored according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) as low, high or unclear (uncertain risk of bias). Two authors (AV and IS) would have graded the methodological quality independently. In case of disagreement, a third author would have been consulted for resolution by consensus. We would have performed a sensitivity analysis on the basis of methodological quality according to the presence or absence of allocation concealment and other aspects of quality.

Data synthesis

We would have calculated relative risks from dichotomized proportional data for each study. The pooled relative risk estimate was to be calculated to assess the overall efficacy of the studies using the Review Manager software (RevMan 2008). Heterogeneity of data would have been quantified by I^2 analysis (Higgins 2003). If this analysis had shown heterogeneity to be low (I^2 smaller than or equal to 25%), we would have used the Mantel-Haenszel risk ratio. Otherwise, we would have carried out sensitivity analyses first to explore the plausible cause of the heterogeneity of data. If heterogeneity was not due to differences between identifiable and separable sub-groups of studies, we would have employed the random-effects model of DerSimonian and Laird (DerSimonian 1986). We would have calculated standardised mean differences (SMD) from the mean changes in disability scores and MRC scores for each study. The weighted pooled SMD were to be calculated for all studies. We were to derive standard deviations for each study by calculation or extraction from the available data. If necessary we would have asked authors for the original data. For all analyses, we would determine 95% confidence intervals.

We would have performed subgroup analyses to explore possible differences in treatment efficacy between patients younger than 65 years and 65 years and older, and between patients with a nadir of neurological deficits within or after twelve months from the onset of symptoms and signs.

RESULTS

Description of studies

For this updated review the number of studies found by the new, current search strategies were: MEDLINE 458 (138 new), EMBASE 518 (142 new), Cochrane Neuromuscular Disease Specialized Register 28 (19 new), Cochrane Central Register of Controlled Trials (CENTRAL) 71 (14 new) and ISI Web of Knowledge 452 (164 new). We identified and assessed 30 studies (6 new) for possible inclusion in the review. Thirteen studies did not show separate data for patients with idiopathic (poly)neuropathy (De

Grandis 1995; Husstedt 1993; Kishore-Kumar 1989; Li 2010; Low 1995; Morley 2003; Otto 2008; Sindrup 1999a; Sindrup 1999b; Sindrup 2001; Sindrup 2003; Vrethem 1997; Wallace 2000), fourteen studies included patients with neuropathic pain and painful (poly)neuropathy of various, unspecified or unclear origin (Frank 2008; Galer 2000; Ho 2008; Huge 2010; Langohr 1982; Maier 2002; Meier 2003; Nurmikko 2007; Onofrj 1995; Otto 2004; Rauck 2006; Rowbotham 2003; Semenchuck 2001; Wallace 2002), three studies did not include useful outcome measures (Bradley 1988; De Grandis 1995; Husstedt 1993), and two studies concerned patients with painful idiopathic small fiber predominant neuropathy (Ho 2009; Windebank 2004). In none of the assessed studies did the patients with idiopathic (poly)neuropathy fulfil our criteria for CIAP. Thus, all studies were excluded for this review update. Details of all the excluded studies are shown in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

There were no studies of sufficient quality that could be included.

Effects of interventions

Analyses could not be performed because no studies were included.

DISCUSSION

Even though 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 patients 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), no clear benefit of treatment with oral prednisone or intravenous immunoglobulin was observed (Vrancken 2004). 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 (Dyck 2007; Nebuchennykh 2008; Smith 2008a; Ziegler 2008a), although in follow-up studies patients with CIAP did not develop diabetes (Jann 2001; Notermans 1994; Vrancken 2002). Chronic obstructive pulmonary disease, subtle cobalamin deficiency, cardiovascular disease or associated risk factors such as hypertriglyceridaemia, hypertension, obesity, or the metabolic syndrome have been implicated in predisposing to the development of axonal polyneuropathy without a cause, i.e. idiopathic or cryptogenic axonal polyneuropathy (Herman 2007; Hughes 2004; Jann 1998; Poza 1997; Saperstein 2003; Smith 2008b; Teunissen 2002; Ziegler 2008a). The microvascular changes in nerve biopsies of patients 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 cardiovascular disease or diabetes are worth considering (Cameron 2001; Eliasson 2003; Forrest 1997; Malik 2000; Smith 2006). Alpha-lipoic acid and prostaglandin E1 have been shown to improve dysfunction of the vasa nervorum and sensory symptoms in diabetic polyneuropathy (Ziegler 2008b), and Cochrane reviews on these topics are in preparation (Li 2006; Mirza 2005). Vitamin B treatment for polyneuropathy is the subject of another Cochrane review (Ang 2008).

One alternative approach would be to test neurotrophic factors (Fressinaud 2003; 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 2007). Neuroimmunophilin ligands such as tacrolimus derivatives without immunosuppressive properties or Rho kinase inhibitors also have neuroprotective and neuroregenerative activity (Gold 2000; Gold 2004; Müller 2005). 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 perhaps form treatment options in the future, but to date no studies 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 patients with CIAP (Erdmann 2010). Treatment of neuropathic pain is the subject of various Cochrane reviews (Challapalli 2005; Derry 2009; Hollingshead 2006; Eisenberg 2006; Lunn 2009; Moore 2009; Saarto 2007; Wiffen 2005a; Wiffen 2005b; Wiffen 2007), and evidence based guidelines including the cost-effectiveness of therapy have been proposed (Attal 2010; Cepeda 2006; Dworkin 2010; Finnerup 2007). With increased understanding of the role of ion channels in neuropathic pain, new therapeutic agents aimed at these ion chan-

nels are emerging and could be worth considering (Dray 2008; Markman 2006; Ossipov 2005).

Some patients have foot drop for which ankle foot orthoses and other rehabilitative measures can be useful. Although not directly relevant to this review of drug therapy, a Cochrane review on this topic is available (Sackley 2007). The effect of exercise in peripheral neuropathy is the subject of a Cochrane review (White 2004), and interventions for fatigue will be evaluated in another (White 2009). Efficacious 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 selection of a sensitive disability outcome measure as being more directly relevant to patients' needs than an electrophysiological, pathological or impairment measure. Even though we preferred the modified Rankin scale for this review, a scale with more steps which is designed for measuring disability in peripheral neuropathy might be superior. Disability scores designed to measure upper and lower limb disability that have been validated for assessing change and which reflect the patients' judgment in inflammatory neuropathies should be considered (Graham 2006a; Merkies 2006). Alternatively, since most patients 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 patients with CIAP demonstrated stabilisation within the first five years after disease onset (Dyck 1981; McLeod 1984; Grahmann 1991; Notermans 1994; Jann 2001; Vrancken 2002). 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 treatments which are not hampered by serious side-effects and are inexpensive.

AUTHORS' CONCLUSIONS

Implications for practice

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

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.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
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.
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
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)
Huge 2010	Neuropathic pain of various origins, including unspecified painful polyneuropathy (i.e. not defined as CIAP)
Husstedt 1993	No separate analyses for idiopathic polyneuropathy. Idiopathic polyneuropathy not well defined (i.e. not defined as CIAP). No useful outcome measures.
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)
Nurmikko 2007	Neuropathic pain of various or unclear origins, including unspecified peripheral neuropathy (i.e. not defined as CIAP)

(*Continued*)

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)
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)
Semenchuck 2001	Neuropathic pain of various origins, including peripheral neuropathy (i.e. not defined as CIAP)
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)
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)
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.

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MEDLINE OvidSP search strategy

1. randomized controlled trial.mp.
2. controlled clinical trial.mp.
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.
4. (trial or placebo or dummy or sham or random$).tw.
5. (drug therapy or "therapeutic use").fs.
6. 2 or 3
7. 4 and 6
8. 1 or 7
9. 5 and 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. chronic idiopathic axonal polyneuropath$.tw.
13. (ciap and axonal).tw.
14. (chronic adj10 axonal neuropath$).tw.
15. (chronic adj10 axonal polyneuropath$).tw.
16. ((axonal or cryptogenic or idiopathic) adj10 neuropath$).tw.
17. ((axonal or cryptogenic or idiopathic) adj10 polyneuropath$).tw.
18. 12 or 13 or 14 or 15 or 16 or 17
19. exp polyneuropathies/ or polyneuropath$.tw.
20. peripheral neuropath$.tw.
21. 19 or 20
22. (painful or neuropathic pain).tw.
23. 21 and 22
24. 18 or 23
25. (11 and 22) not painful.tw.
26. 11 and 24
27. 25 or 26
28. limit 27 to yr="1981 -Current"
29. ..dedup 28

Appendix 2. EMBASE (www.embase.com) search strategy

No.	Query
#28	#11 AND #26 AND [embase]/lim AND [1981-2010]/py
#27	#11 AND #26
#26	#22 OR #23 OR #25
#25	#22 AND #24
#24	'neuropathic pain'
#23	painful NEXT/10 (neuropath* OR polyneuropath*)
#22	#16 OR #21
#21	#17 AND #20
#20	#18 OR #19
#19	cause* OR etiolog* OR origin AND (unknown OR 'without known' OR 'with no known' OR various OR variable OR different)
#18	cryptogenic OR idiopathic
#17	polyneuropathy OR 'peripheral neuropathy' OR 'sensorimotor neuropathy' OR 'sensory neuropathy'
#16	#12 OR #13 OR #14 OR #15
#15	(axonal OR idiopathic OR cryptogenic) NEXT/10 (neuropath* OR polyneuropath*)
#14	chronic NEXT/10 ('axonal neuropathy' OR 'axonal neuropathies' OR 'axonal polyneuropathy' OR 'axonal polyneuropathies')
#13	ciap AND axonal
#12	'chronic idiopathic axonal' NEXT/1 (neuropath* OR polyneuropath*)
#11	#9 NOT #10
#10	'nonhuman'/exp NOT 'human'/exp
#9	#5 AND #8
#8	#1 OR #7
#7	#4 AND #6
#6	#2 OR #3

(*Continued*)

#5	'drug therapy':de,lnk,cl
#4	trial OR placebo OR dummy OR sham OR random*
#3	'crossover procedure' OR 'comparative effectiveness' OR 'factorial design' OR 'single blind procedure' OR 'double blind procedure' OR 'triple blind procedure' OR 'study design'
#2	'controlled clinical trial'
#1	'randomized controlled trial'

Appendix 3. The Cochrane Central Register of Controlled Trials search strategy

#1 chronic idiopathic axonal polyneuropathy
#2 ciap
#3 chronic NEAR/3 (axonal polyneuropathy OR axonal neuropathy)
#4 (axonal OR idiopathic OR cryptogenic) NEAR (polyneuropathy OR neuropathy)
#5 #1 OR #2 OR #3 OR #4
#6 (polyneuropathy OR "peripheral neuropathy")
#7 "painful neuropathy" OR "painful polyneuropathy" OR "neuropathic pain"
#8 #6 AND #7
#9 #5 OR #8
#10 (random* OR placebo* OR crossover OR cross over) NEAR (trial OR study)
#11 #9 AND #10

Appendix 4. ISI Web of Knowledge search strategy

Limits: Databases=SCI-EXPANDED, CPCI-S Timespan=1981-2010
#1 TS=(random* trial) OR TS=(random* study) OR TS=(random* treatment) OR TS=(randomi* therap*)
#2 TS=(placebo) OR TS=(blind*) OR TS=(control*) OR TS=(crossover) OR TS=(cross-over)
#3 TS=(trial) OR TS=(study) OR TS=(treatment) OR TS=(treated) OR TS=(therap*)
#4 TS=(random*)
#5 #2 SAME #3
#6 #1 OR #5
#7 #4 AND #6
#8 TS=(idiopathic neuropath*) OR TS=(idiopathic polyneuropathy) OR TS=(cryptogenic neuropath*) OR TS=(cryptogenic polyneuropathy) OR TS=(chronic idiopathic axonal polyneuropathy)
#9 TS=(neuropath*) OR TS=(polyneuropathy)
#10 TS=(idiopathic) OR TS=(cryptogenic)
#11 TS=((cause* OR etiolog* OR origin) SAME (unknown OR without OR various OR variable OR different))
#12 #9 SAME #10
#13 #9 SAME #11
#14 #8 OR #12 OR #13
#15 TS=painful OR TS=(neuropathic pain)
#16 TS=(neuropathy OR polyneuropathy)
#17 #15 SAME #16
#18 #14 OR #17
#19 #7 AND #18

WHAT'S NEW

Last assessed as up-to-date: 15 February 2011.

Date	Event	Description
4 March 2013	Amended	Added Published notes concerning the next scheduled update of this review.

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 2, 2004

Date	Event	Description
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 also extracted data. All authors contributed to subsequent drafts and agreed the final version.

DECLARATIONS OF INTEREST

None.

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

For the 2011 update we revised the risk of bias methods section according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

NOTES

New evidence on this topic is slow to emerge. The next update of the review is planned for 2015, which is four years after the last search rather than the usual two years. If new trials are published in the interim an earlier update will be scheduled.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Aged; Humans