Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an overview of systematic reviews

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What's new

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Abstract

Background

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic progressive or relapsing and remitting disease that usually causes weakness and sensory loss. The symptoms are due to autoimmune inflammation of peripheral nerves. CIPD affects about 2 to 3 per 100,000 of the population. More than half of affected people cannot walk unaided when symptoms are at their worst. CIDP usually responds to treatments that reduce inflammation, but there is disagreement about which treatment is most effective.

Objectives

To summarise the evidence from Cochrane systematic reviews (CSRs) and non-Cochrane systematic reviews of any treatment for CIDP and to compare the effects of treatments.

Methods

We considered all systematic reviews of randomised controlled trials (RCTs) of any treatment for any form of CIDP. We reported their primary outcomes, giving priority to change in disability after 12 months.

Two overview authors independently identified published systematic reviews for inclusion and collected data. We reported the quality of evidence using GRADE criteria. Two other review authors independently checked review selection, data extraction and quality assessments.

On 31 October 2016, we searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (in the *Cochrane Library*), MEDLINE, Embase, and CINAHL Plus for systematic reviews of CIDP. We supplemented the RCTs in the existing CSRs by searching on the same date for RCTs of any treatment of CIDP (including treatment of fatigue or pain in CIDP), in the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL Plus.

Main results

Five CSRs met our inclusion criteria. We identified 23 randomised trials, of which 15 had been included in these CSRs. We were unable to compare treatments as originally planned, because outcomes and outcome intervals differed.

Corticosteroids

It is uncertain whether daily oral prednisone improved impairment compared to no treatment because the quality of the evidence was very low (1 trial, 28 participants). According to moderate-quality evidence (1 trial, 41 participants), six months' treatment with high-dose monthly oral dexamethasone did not improve disability more than daily oral prednisolone. Observational studies tell us that prolonged use of corticosteroids sometimes causes serious side-effects.

Plasma exchange

According to moderate-quality evidence (2 trials, 59 participants), twice-weekly plasma exchange produced more short-term improvement in disability than sham exchange. In the largest observational study, 3.9% of plasma exchange procedures had complications.

Intravenous immunoglobulin

According to high-quality evidence (5 trials, 269 participants), intravenous immunoglobulin (IVIg) produced more short-term improvement than placebo. Adverse events were more common with IVIg than placebo (high-quality evidence), but serious adverse events were not (moderate-quality evidence, 3 trials, 315 participants). One trial with 19 participants provided moderate-quality evidence of little or no difference in short-term improvement of impairment with plasma exchange in comparison to IVIg. There was little or no difference in short-term improvement of disability with IVIg in comparison to oral prednisolone (moderate-quality evidence; 1 trial, 29 participants) or intravenous methylprednisolone (high-quality evidence; 1 trial, 45 participants). One unpublished randomised open trial with 35 participants found little or no difference in disability after three months of IVIg compared to oral prednisone; this trial has not yet been included in a CSR. We know from observational studies that serious adverse events related to IVIg do occur.

Other immunomodulatory treatments

It is uncertain whether the addition of azathioprine (2 mg/kg) to prednisone improved impairment in comparison to prednisone alone, as the quality of the evidence is very low (1 trial, 27 participants). Observational studies show that adverse effects truncate treatment in 10% of people.

According to low-quality evidence (1 trial, 60 participants), compared to placebo, methotrexate 15 mg/kg did not allow more participants to reduce corticosteroid or IVIg doses by 20%. Serious adverse events were no more common with methotrexate than with placebo, but observational studies show that methotrexate can cause teratogenicity, abnormal liver function, and pulmonary fibrosis.

According to moderate-quality evidence (2 trials, 77 participants), interferon beta-1a (IFN beta-1a) in comparison to placebo, did not allow more people to withdraw from IVIg. According to moderate-quality evidence, serious adverse events were no more common with IFN beta-1a than with placebo.

We know of no other completed trials of immunosuppressant or immunomodulatory agents for CIDP.

Other treatments

We identified no trials of treatments for fatigue or pain in CIDP.

Adverse effects

Not all trials routinely collected adverse event data; when they did, the quality of evidence was variable. Adverse effects in the short, medium, and long term occur with all interventions. We are not able to make reliable comparisons of adverse events between the interventions included in CSRs.

Authors' conclusions

We cannot be certain based on available evidence whether daily oral prednisone improves impairment compared to no treatment. However, corticosteroids are commonly used, based on widespread availability, low cost, very low-quality evidence from observational studies, and clinical experience. The weakness of the evidence does not necessarily mean that corticosteroids are ineffective. High-dose monthly oral dexamethasone for six months is probably no more or less effective than daily oral prednisolone. Plasma exchange produces short-term improvement in impairment as determined by neurological examination, and probably produces short-term improvement in disability. IVIg produces more short-term improvement in disability than placebo and more adverse events, although serious side effects are probably no more common than with placebo. There is no clear difference in short-term improvement in impairment with IVIg when compared

with intravenous methylprednisolone and probably no improvement when compared with either oral prednisolone or plasma exchange. According to observational studies, adverse events related to difficult venous access, use of citrate, and haemodynamic changes occur in 3% to17% of plasma exchange procedures.

It is uncertain whether azathioprine is of benefit as the quality of evidence is very low. Methotrexate may not be of benefit and IFN beta-1a is probably not of benefit.

We need further research to identify predictors of response to different treatments and to compare their long-term benefits, safety and cost-effectiveness. There is a need for more randomised trials of immunosuppressive and immunomodulatory agents, routes of administration, and treatments for symptoms of CIDP.

Plain language summary

Overview of all systematic review of all treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Review question

What can we learn from summarising the evidence from systematic reviews on treatments for **C**hronic **I**nflammatory **D**emyelinating **P**olyradiculoneuropathy (CIDP)? Is any treatment more or less effective and safe than another?

Background

CIDP is a long-term condition, in which symptoms can steadily worsen over time or show periods of improvement and relapse. People usually have weakness and numbness due to inflammation of nerves (nerves affected are outside the spinal cord and brain). CIDP affects about 2 to 3 per 100,000 of the population and can be disabling. More than half of affected people cannot walk unaided when symptoms are at their worst. Treatments directed at reducing the inflammation usually help but there is no clear evidence favouring one commonly used treatment over another.

Methods

We searched five databases for all systematic reviews and randomised controlled trials (RCTs) until October 2016. We judged that five Cochrane systematic reviews (CSRs) provided the best evidence and identified 23 randomised trials, of which 16 have so far been included in CSRs. We assessed the quality of their included evidence.

Key results and quality of the evidence

The evidence from randomised trials is as follows.

1. It is uncertain whether daily oral prednisone (an anti-inflammatory corticosteroid) improved weakness and sensation (numbness) compared to no treatment, as the evidence is of very low quality. We know that corticosteroids have a significant risk of serious side effects during prolonged use.

2. High-dose monthly oral dexamethasone (a more powerful corticosteroid) for six months was probably no more or less effective than daily oral prednisolone.

3. Plasma exchange probably produced significantly more short-term improvement in disability than dummy exchange. In the largest observational study, 3.9% of plasma exchange procedures had complications.

4. IVIg produced significantly more short-term improvement in disability than placebo. Adverse events were more common with IVIg than placebo but serious adverse events were probably no more common than with placebo. Other, lower-quality studies, not eligible for inclusion here, report that serious adverse effects can occur with IVIg.

5. There was no clear difference in short-term improvement of impairment with plasma exchange as compared to IVIg.

6. There was probably little or no difference in short-term improvement of disability with IVIg in comparison to oral prednisolone and there was little or no difference in comparison to intravenous methylprednisolone. Corticosteroids are much more widely available than IVIg, and are cheaper and easier to use.

7. It is uncertain whether low-dose azathioprine added to prednisone improved impairment over prednisone alone, because the quality of evidence is very low. Adverse events were not reported but observational studies show that side effects prevent 10% of people from continuing treatment.

8. Methotrexate may have no benefit over placebo in number of participants able to reduce their corticosteroid or IVIg dose by 20%. Serious adverse events were probably no more common with methotrexate than with placebo. We know from other types of study that methotrexate has serious side-effects, including damage to fetuses, liver function abnormalities and scarring of the lung.

9. Interferon beta-1a (IFN beta-1a), compared to placebo, probably does not allow more people to withdraw from IVIg. Serious adverse events were probably no more common with IFN beta-1a than with placebo in the two studies of this intervention.

10. There have been no other completed trials of medicines that suppress or change immune responses or that treat fatigue or pain in CIDP.

We need further research on predictors of response to different treatments, on long-term benefits, and of cost-effectiveness. We need more RCTs of medicines that suppress or change immune responses and treat symptoms of pain and fatigue in CIDP, and better ways to collect information on adverse events.

This review is up to date to October 2016.

Background

Description of the condition

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic progressive or relapsing and remitting disease that usually causes weakness, sensory loss, and neuropathic pain in the limbs (Vallat 2010). It is caused by inflammation of the peripheral nervous system that damages the myelin sheaths that insulate nerve fibres. This process produces 'demyelination' within affected nerves, which slows and can block signal conduction. Although repeated episodes of demyelination and remyelination are the predominant pathology, the inflammation also damages the axons in the core of nerve fibres, which can cause the axons to degenerate. The motor and sensory spinal nerve roots and peripheral nerves are most often affected. The cranial nerves that control eye movements and facial, swallowing, and speech muscles are less often involved. CIDP usually spares the nerves that supply muscles of respiration and the autonomic nerves that control the bladder, bowel, and circulation. CIDP often causes chronic fatigue.

The diagnosis is made by a combination of clinical signs and symptoms, evidence of demyelination on nerve conduction tests, and by excluding other causes. Sometimes supportive tests, such as cerebrospinal fluid analysis, magnetic resonance imaging of spinal nerve roots and nerve trunks, nerve biopsy, and therapeutic trials of immunomodulating agents, help confirm the diagnosis. Several diagnostic criteria have been proposed. The most widely accepted criteria used in recent clinical trials rely on clinical history, examination, nerve conduction evidence, and exclusion of other causes (Van den Bergh 2010).

The prevalence of CIDP ranges between one and nine people with CIDP per 100,000 population in different studies, with most studies reporting two to three people per 100,000 (Mahdi-Rogers 2010). The condition was 1.4 to 4.7 times more common in men than women in eight population-based studies that reported sex ratios. The average age of onset in the four population-based studies that provided these data was 48 years to 58 years (Mahdi-Rogers 2010). CIDP is rare in children and becomes more common with age, reaching peak prevalence in the eighth decade. In one population-based study, nine of 62 people (14.5%) had a progressive course, 44 people (71%) had a relapsing-remitting course, and nine people (14.5%) had a monophasic disease course (Mahdi-Rogers 2010). According to a summary of series by Vallat 2010, other studies find that 7% to 50% of people with CIDP have monophasic or progressive courses, and 20% to 35% of people have a relapsing-remitting course.

CIDP can be severely disabling, but the degree of disability varies. On the prevalence day in the population-based study (Mahdi-Rogers 2010), 28 people (68.2%) walked independently, 10 people (24.4%) required unilateral support and three people (7.3%) required bilateral support to walk 10 metres. No-one in the study needed a wheelchair, although in other series some people did. At nadir, 31 people (75.6%) had disability in their upper limbs, 17 people (41.5%) could walk independently, 11 people (26.8%) needed unilateral support, six people needed bilateral support and seven people used a wheelchair. Most commonly, CIDP causes progressive weakness leading to a need for aids to walk, which is often followed by improvement with treatment. However, repeated or prolonged treatment may be needed. In the population-based study mentioned, 64 of 84 people (76.2%) required treatment and 51 people (79.7%) improved with at least one of the main treatments: corticosteroids, intravenous immunoglobulin (IVIg), or plasma exchange. Treatment of CIDP is expensive, especially when IVIg is used. According to Blackhouse 2010, the cost per quality-adjusted life year (QALY) of using IVIg rather than corticosteroids was CAD 696,598 (approximately USD 535,800).

The causes of CIDP are attributed to immune mechanisms. During active disease, pathological study of affected nerve roots and trunks shows inflammation and stripping of the myelin sheaths from the axons by macrophages. The inflammation is probably due to an autoimmune process. There is debate about the relative roles of antibodies and T-lymphocytes directed against the Schwann cell, myelin, or both. There is some evidence of impairment of the regulatory T and B cells that normally effect autoimmune responses (Vallat 2010; Mathey 2015). Specific serum autoantibodies, which include antibodies to gangliosides and other components of myelin, are present only in a small proportion of people with CIDP. People who have autoantibodies to components of the node of Ranvier, such as contactin-1/contactin-associated protein 1 (CNTN1/CASPR), or neurofascin IgG4 autoantibodies, seem to have more aggressive disease and a poorer response to treatment (Querol 2014).

Description of the interventions

Treatments aimed at the underlying disease

The common two first-line treatments for CIDP are corticosteroids, which are given daily as tablets, or every four weeks as tablets or intravenous infusions, and immunoglobulin, which is usually given intravenously over two to five days for the first dose and then over one day every two to eight weeks for follow-up doses. Corticosteroids are anti-inflammatory drugs used in many types of inflammatory conditions, such as asthma and arthritis. They are widely available and inexpensive, but long-term use risks potentially serious side-effects, including high blood pressure, diabetes mellitus, obesity, thinning of the bones, and cataracts (Bromberg 2004).

Immunoglobulin has both different risks and different advantages. It is extracted from the plasma of several thousand blood donors and purified to reduce the risk of transmitting infections. It is in limited supply, not always available, and extremely expensive. Immunoglobulin causes two categories of adverse events: transient and long-lasting. Infusions are commonly associated with several days or a week of headache, nausea, rash, or influenza-like symptoms, Some people develop signs of meningeal irritation. In contrast, serious or long-lasting side-effects are rare. They include venous thrombosis, which can cause infarctions in important organs such as the brain, lungs, and heart; severe skin

reactions; haemolytic anaemia; and kidney failure (Eftimov 2013). Immunoglobulin is most often administered intravenously, but there is an increasing trend to subcutaneous administration, which is generally more convenient for patients.

Plasma exchange is the third first-line treatment. It involves removing the patient's blood, separating the plasma from the cells, replacing the plasma with a substitute, and returning the cells and plasma substitute to the patient. Modern machines can replace the whole plasma volume in a few hours. A course of about five treatments on consecutive or alternate days is commonly used to initiate treatment, but regimens vary, and single exchanges every few weeks are sometimes used for long-term treatment. Plasma exchange is usually safe, although there are side-effects, such as bleeding, infections, and injuries arising from inserting large tubes into veins. Its main drawbacks are inconvenience, expense, and limited availability (Kiprov 2001).

When first-line treatments are inadequate, neurologists often prescribe immunosuppressant or other immunomodulatory agents. Those most commonly used for CIDP are azathioprine, cyclophosphamide, ciclosporin, and methotrexate. The drugs can be given orally, although cyclophosphamide is also given intravenously and methotrexate by intramuscular or subcutaneous injection. They all reduce the white cell count and increase the risk of infection. A small long-term increased risk of cancer is also a concern. Individual agents have idiosyncratic side-effects. For instance, azathioprine can cause hypersensitivity reactions, cyclophosphamide hair loss, and ciclosporin kidney failure or hypertension. Methotrexate can harm fetal growth and cause liver dysfunction. Mycophenolate mofetil can cause diarrhoea and abdominal pain. Newer immunosuppressant drugs that target specific components of the immune system include rituximab, which depletes circulating B cells, and fingolimod, which prevents activated T cells from leaving lymph nodes. The potential benefits of each treatment have to be balanced against possible harms, and the risk of non-treatment or other treatment options (Markvardsen 2013).

Treatments of symptoms

In addition to considering treatments for underlying disease processes, we planned to provide an overview of reviews of treatments for symptoms of CIDP, including neuropathic pain and fatigue. Drugs that have undergone trials as treatments for neuropathic pain include the tricyclic drug amitriptyline (Saarto 2007) and drugs that bind to the alpha-2-delta calcium channel, gabapentin (Moore 2014) and pregabalin (Moore 2009). These are given orally. Tricyclics are inexpensive and widely available. Drugs and exercise have been used to treat fatigue in peripheral neuropathy (White 2014). This overview aimed to focus on reviews and trials specific to CIDP.

How the intervention might work

Corticosteroids, IVIg, and other immunomodulatory therapies are believed to treat CIDP by inhibiting one or many immune components of its presumed autoimmune inflammatory process. The mechanisms are incompletely understood, in part because the mechanisms of nerve damage in CIDP are themselves not understood (Vallat 2010; Mathey 2015). The respective Cochrane Systematic Reviews (CSRs) describe in more detail the ways in which corticosteroids, IVIg, and immunosuppressant drugs are believed to work.

- Corticosteroids suppress multiple genes that are activated in chronic inflammatory diseases, mainly through binding of liganded glucocorticoid receptors to coactivators and recruitment of histone deacetylase-2 (HDAC2) to the activated transcription complex. Higher concentrations of corticosteroids also interact with DNA recognition sites to activate transcription of anti-inflammatory genes.
- Pooled immunoglobulins have multiple modes of action. They interfere with activity of the complement system, which carries out immune-mediated cell damage, and perhaps compete with nerve-targeting autoantibodies believed to be present in CIDP.
- Plasma exchange is thought to work by removing antibodies and other small molecules, such as chemokines, that can affect T cell function.
- Interferon beta (IFN beta) has multiple actions on the immune system which tend to down-regulate harmful immune responses (Kieseier 2011).
- Exercise might help fatigue in CIDP by a combination of improving aerobic fitness, strengthening relevant muscle groups, and positive psychological effects.

Why it is important to do this overview

Treatment of the underlying disease in CIDP is covered by four CSRs, on corticosteroids (Hughes 2015), IVIg (Eftimov 2013), plasma exchange (Mehndiratta 2015), and other immunosuppressive and immunoregulatory drugs (Mahdi-Rogers 2013). Some people with CIDP have abnormal proteins called paraproteins in their blood. Stork 2015, the CSR of treatment for IgA and IgG paraproteinaemic neuropathy, included one relevant trial. CIDP treatment may have been included in other CSRs or non-Cochrane systematic reviews, for instance of neuropathic pain (Saarto 2007; Moore 2009; Moore 2014), fatigue in peripheral neuropathy (White 2014), or exercise for peripheral neuropathy (White 2004). Drawing together the reviews in this overview makes their combined information more accessible to people with CIDP, healthcare professionals, and researchers, and identifies topics for targeting future research.

Objectives

To summarise the evidence from Cochrane systematic reviews and non-Cochrane systematic reviews of any treatment for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and to compare the effects of treatments.

Methods

Criteria for considering reviews for inclusion

Types of reviews

In accordance with the advice on overviews of reviews in the *Cochrane Handbook for Systematic Reviews of Interventions* (Becker 2011), we considered all Cochrane Systematic Reviews (CSRs) and non-Cochrane systematic reviews of randomised controlled trials (RCTs) of any treatment for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). We did not include non-systematic reviews. We defined systematic reviews according to the *Cochrane Handbook for Systematic Reviews of Interventions* as those having:

- pre-defined objectives;
- pre-defined criteria for eligibility of evidence;
- an objective systematic search for evidence applying predetermined inclusion and exclusion criteria; and
- explicit and systematic methods for synthesising evidence which attempt to reduce bias (Higgins 2011).

When we found an RCT of another therapy for which a plausible rationale or empirical basis existed that had not been included in a CSR, we noted the RCT in our overview. We also notified Cochrane Neuromuscular so that the trial can be considered for inclusion in a new or existing CSR and then subsequently in later updates of this overview.

Types of participants

We included reviews of all forms of CIDP approximating to the definite, probable, and possible diagnostic criteria in the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guideline (Van den Bergh 2010). If reviews used other criteria we noted this. There is some evidence that patients who have CIDP associated with paraproteins have different natural history and treatment responses than non-paraproteinaemic cases. We considered including those with IgG or IgA paraproteins, provided that they fulfilled the clinical and electrophysiological criteria of the EFNS/PNS guideline for CIDP. Such participants have been considered in a separate CSR (Stork 2015). We excluded studies of people with IgM paraproteins because their neuropathy has a distinctive pathogenesis, and responds differently to treatment (Lunn 2016). We excluded people with paraneoplastic CIDP-like illness associated with malignancy.

Some RCTs and reviews included a few participants with IgM paraproteins or malignancy. We attempted to exclude the results from these participants. If this was not possible and less than five per cent of participants in a trial had either of these exclusion criteria, we included the trial. If more than five per cent of participants had these causes, we excluded the trial from our primary analysis but included it in a sensitivity analysis.

If systematic reviews also included trials involving participants with forms of peripheral nerve disease other than CIDP, we tried to obtain the results of participants with CIDP alone. If this was not possible, and more than 95% of participants fulfilled the inclusion criteria for this overview, we included the trial. If there were fewer than 95% of participants with CIDP we would have excluded the trial from our primary analysis but included it in a sensitivity analysis.

Types of interventions

We planned to include all interventions for CIDP, whether pharmacological or physical. We considered treatments of both the underlying disease process and of two important CIDP symptoms, pain and fatigue.

Types of outcomes

In the narrative part of this overview, we reported the outcomes reported in the individual CSRs. We gave priority to "change in disability after 12 months" as the primary efficacy outcome, with change after six months as an alternative. We also reported short-term outcomes after periods of two weeks to six months, since most trials only reported these short-term outcomes. The scales used must have been validated as having good reproducibility, face validity and correlation with other scales measuring the same attribute. Recent studies have used the Inflammatory Neuropathy Cause and Treatment (INCAT) scale (Hughes 2001), Overall Disability Sum Score (ODSS) (Merkies 2002), and Overall Neuropathy Limitations Scale (ONLS) (Graham 2006). Earlier studies have used the Modified Rankin Scale (Bamford 1989) and Guillain-Barré Syndrome Disability Scale (Hughes 1978).

The preferred secondary efficacy outcomes were change in impairment scores and in quality of life. The scales used must have been validated as having good reproducibility, face validity and correlation with other scales measuring the same attribute. We anticipated that most studies would have included the Medical Research Council (MRC) sum score (Kleyweg 1991) and a sensory sum score (Merkies 2000), or the Mayo Clinic Neuropathy Impairment Scale (NIS) (Dyck 2005).

We reported serious adverse events, defined as those requiring prolonged hospitalisation or which were fatal at any time during treatment or within a biologically plausible time after treatment cessation. We expected all trials to have collected these events and systematic reviews to have reported them. We also reported adverse events which, although not serious, could influence treatment choices. Examples include diabetes mellitus (relevant for corticosteroids), skin rash (IVIg) and abnormal liver function (methotrexate).

Search methods for identification of studies

On 31 October 2016, we searched the Cochrane Database of Systematic Reviews (CDSR 2012, Issue 12) and the Database of Abstracts of Reviews of Effects (DARE 2015, Issue 2) (in *The Cochrane Library*), MEDLINE (January 1966 to October 2016), Embase (January 1980 to October 2016) and CINAHL Plus (January 1937 to October 2016) for systematic reviews of CIDP. We supplemented the RCTs in the existing CSRs by searching for RCTs of any treatment of CIDP which included

treatment of fatigue or pain in CIDP, in the Cochrane Neuromuscular Specialised Register (31 October 2016), Cochrane Central Register of Controlled Trials (CENTRAL) (31 Ocober 2016 in the *Cochrane Register of Studies Online*), MEDLINE (January 1966 to October 2016), Embase (January 1980 to October 2016) and CINAHL Plus (January 1937 to October 2016).

The detailed search strategies are in the appendices: Appendix 1 (DARE), Appendix 2 (MEDLINE), Appendix 3 (Embase), Appendix 4 (CINAHL Plus), Appendix 5 (Cochrane Neuromuscular Specialised Register), and Appendix 6 (CENTRAL).

Data collection and analysis

RACH, MPTL, and IvS completed the first draft of this Overview of Reviews. To reduce the risk of bias arising from review authorship, trial authorship, or financial conflicts of interest, two independent authors (ALO and CC) extensively checked and edited the review.

Selection of reviews

Two overview authors (RACH and MPTL or INvS) first independently selected systematic reviews for inclusion in April 2014. They would have resolved disagreements by reference to a third overview author, but there were no disagreements. CC and ALO subsequently independently checked the search results and an updated search and selected any new systematic reviews to be included. These authors retained the systematic reviews already identified, unless a review had been updated in the interim. The overview authors included only the most up-to-date version of each review.

Data extraction and management

Two overview authors (CHC and ALO) independently collected data from published systematic reviews with a data collection form designed specifically to include all the data needed. We contacted the review authors or extracted data from the relevant trials ourselves if information was lacking. ALO and CC checked the data.

Assessment of methodological quality of included reviews

The two authors of this overview update (CHC and ALO) independently assessed the methodological quality of each included review. For this purpose they used the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool developed by Shea 2007, which has been shown to have acceptable inter-rater agreement, construct validity and feasibility (Shea 2009). They reached agreement by discussion.

We reported the assessment of the review authors about the quality of their included evidence according to GRADE criteria. GRADE has become the method preferred by Cochrane for evaluating the quality of evidence, and by many guideline bodies for assessing the strength of recommendations (GRADE 2008; Guyatt 2008). Assessments of quality of evidence can be 'high', 'moderate', 'low' or 'very low'. Assessments are based on five factors that can decrease the quality level of the body of evidence and three that can increase the quality level. Reasons to downgrade RCTs from high quality are: 1. risk of bias, 2. indirectness of evidence, 3. unexplained heterogeneity, 4. imprecision (wide CIs), and 5. a high probability of publication bias. Reasons to upgrade evidence are 1. a large effect size, 2. when "all plausible confounding factors would reduce a demonstrated effect or suggest a spurious effect when results show no effect" and 3. a dose-response gradient (Schünemann 2011). If the grading of the strength of evidence by the original review authors seemed to us questionable, we adjusted the grade to achieve consistency between reviews, and explained our reasons.

Data synthesis

We anticipated that the principal method for presenting data from the constituent systematic reviews would be a narrative review. We reported the evidence for each intervention from each review and its strength, estimated using the GRADE approach. If we had found more than one eligible review of a particular intervention and the conclusions agreed, we would have reported this. Where the conclusions differed we would have explored the reasons for any difference in relation to the AMSTAR scores of the included reviews. In fact there were no other eligible reviews (see below).

Appendix 7 details methods for use if a network meta-analysis had been possible, as described in the protocol (Hughes 2013).

Results

Results of the search

The searches identified potential RCTs and systematic reviews. The total number of papers found in each database was 658 in MEDLINE, 299 in Embase, 3 in CINAHL Plus, 110 in the Cochrane Neuromuscular Specialised Register, 130 in CENTRAL and 4 in DARE. See Figure 1.

Description of included reviews

We selected the most recent updates of Cochrane Systematic Reviews (CSRs) of corticosteroids (Hughes 2015), intravenous immunoglobulin (IVIg) (Eftimov 2013), plasma exchange (Mehndiratta 2015), and other immunomodulatory treatments (Mahdi-Rogers 2013) for treating chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) for inclusion in this overview. In accordance with our protocol we also included the most recent update of a CSR of treatment for neuropathy associated with IgA and IgG paraproteins (Stork 2015), but not those associated with IgM paraproteins (Lunn 2016). All the identified CSRs fulfilled the inclusion criteria for this overview and received favourable answers to all questions in the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) checklist whenever applicable (Table 1). We inspected non-Cochrane reviews published since

2004 if the title and abstract suggested they might have fulfilled the inclusion criteria. However, none fulfilled the criterion of having pre-defined objectives (Table 2), thus we did not include them.

Search for additional randomised controlled trials

Two review authors (RACH and MPTL) scrutinised the titles and abstracts retrieved by the search for this review. They identified 22 completed trials. They detected one additional trial in one of the parent reviews that was not retrieved by this search (Dyck 1991). Thus, the overview authors considered 23 trials (see Table 3). Of these, two trials of IVIg were excluded from the CSRs and from this review because of a high risk of bias: one because it randomised participants who were known responders to IVIg (Van Doorn 1990) and one because 50% of participants were lost to follow-up (Zinman 2005). Six completed trials were not included in any CSR. We mentioned these in the Discussion. They are:

1. An open randomised trial comparing corticosteroids and IVIg that had been presented only in abstract form, but for which the investigator provided results (Camdessanché 2013).
2. A randomised trial comparing gullong tongluo capsule with no treatment (Hu 2009);
3. A trial of lipoic acid NCT00962429;
4. A trial testing 3,4-diaminopyridine for four days (Russell 1995);
5. A comparative trial of two brands of IVIg (Kuitwaard 2010); and
6. A trial comparing IVIg with subcutaneous immunoglobulin (Markvardsen 2013).

Thus altogether the Results section of this overview included 15 randomised controlled trial (RCTs) described in five CSRs.

In addition, sponsors abandoned two trials of IVIg after publication of their designs but before randomisation started; these were Lee 2010 and the POINT trial (Cornblath 2010). Three other trials are still in progress (Table 4).

Two other overview update authors (CHC and ALO) independently scrutinised the titles and abstracts retrieved by the search for this overview. They identified no other new completed trials and agreed the 15 RCTs for inclusion.

Effects of interventions

Corticosteroids

No trial compared corticosteroids with placebo. One RCT assessed the efficacy of corticosteroids versus no treatment (Dyck 1982). Two trials compared two corticosteroid regimens (Eftimov 2012; Van Schaik 2010). Three completed trials compared corticosteroids with IVIg; the CSR of IVIg (Eftimov 2013) includes the two published trials (Hughes 2001; Nobile-Orazio 2012), and we have described a trial presented in only abstract form, which has not been fully published, in the Discussion section of this overview (Camdessanché 2014).

Corticosteroids versus no treatment

Dyck 1982 compared corticosteroids to no treatment (not placebo). The trial recruited 40 participants, but five were withdrawn because of misdiagnosis. Participants were alternately assigned to prednisone or no treatment. In the prednisone group, the dose started at 120 mg every other day and tapered to 0 mg by the end of 12 weeks. Seven participants (five in the treatment group and two in the control group) did not complete the study. Of the five people assigned to prednisone who were excluded, one died from cardiac arrhythmia, attributed possibly to hyperglycaemia, three had their prednisone dosage altered from that allowed by the schedule, and one remained respirator-bound and did not complete follow-up. Referring physicians started two participants in the untreated control group on prednisone because of deterioration in their neurological status. As there was no placebo group, participants were not blinded to the intervention, and the report does not state whether investigators and follow-up assessments were blinded.

Of the 28 participants completing the trial according to the protocol, 14 belonged to each group. The participants in the two groups were well matched for age, sex, initial Neurology Disability Score (NDS, now called the Neuropathy Impairment Score, NIS), muscle strength, cutaneous sensation, nerve conduction values, and cerebrospinal fluid protein. The prednisone group included seven participants with a progressive course and seven participants with a relapsing course. The untreated group comprised 12 participants with a progressive course and two participants with a relapsing course. Data for the preferred primary outcome measure for this overview, change in disability after 12 months, were not available, but we had data for one of our secondary outcome measures, change in impairment after three months. The conclusions are sensitive to whether the analysis includes the participants who did not complete the trial. The trial authors omitted the seven participants who breached their protocol, and reported results for the remainder. In this analysis, after 12 weeks the median change in the NIS (scale range 0 healthy to 280 maximally impaired) was a worsening of 1.5 points in the untreated group and an improvement of 10 points in the prednisone group, which was a significant difference between the groups (P = 0.016). The CSR authors recalculated the results imputing the worst value for each group for the missing values, whereupon the results still favoured prednisone treatment (median change of 2 points worsening in the untreated group and 5 points improvement in the prednisone group), but the difference was not statistically significant. The trial authors' analysis is likely to exaggerate the treatment effect, whilst that of the CSR authors is likely to be conservative. Ideally a technique using more balanced assumptions than either of these approaches, such as multiple imputation or analysis with mixed models, or both, should be used, but this was not possible, as the CSR authors did not have access to individual participant data.

The CSR authors also compared the proportions of participants who improved in impairment, stayed the same, or worsened after 12 weeks. They categorised seven participants who did not complete the trial and were withdrawn as having not improved. With this imputation, the risk ratio (RR) for improvement was 2.02 (95% confidence interval (CI) 0.90 to 4.52) greater with prednisone than no treatment but the result was imprecise, with CI that included the possibility of little or no difference. The trial did not report adverse events in detail but one participant randomised to corticosteroids died and another

developed hyperglycaemia and was withdrawn.

The CSR authors considered that this one trial provided only very low-quality evidence about the efficacy of daily oral prednisone compared with no treatment, and that the trial had a high risk of bias due lack of allocation concealment, lack of blinding, and the absence of an intention-to-treat analysis. It was not possible to comment on a possible increase in harms. The weakness of the evidence does not necessarily mean that corticosteroids are ineffective and, as explained in the Discussion, corticosteroids are widely used.

Comparison of daily standard dose with high-dose monthly corticosteroids

One parallel-group, double-blind RCT (the PREDICT trial) randomised 41 participants between two different corticosteroid regimens (Van Schaik 2010). One group received a standard oral prednisolone regimen for 32 weeks, starting with 60 mg daily for five weeks and then gradually tapering to zero by week 32. The other group received high-dose monthly oral dexamethasone for six months, given as 40 mg daily for four days followed by placebo for 24 days. The primary outcome defined by the trial authors was reaching and remaining in remission without treatment at 12 months. Remission was defined as a minimum three-point improvement on the Rivermead Mobility Index and a minimum one-point improvement in the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale. If a participant did not show improvement or disease stabilisation compared with baseline at eight weeks, relapsed, or had serious side-effects, trial treatment was stopped and the participant was considered a treatment failure. The CSR authors felt that this trial had a low risk of bias because of randomisation, careful allocation concealment, and identical appearance of medication in both groups.

Twenty-four participants were assigned to dexamethasone and 16 to prednisolone. The dexamethasone and prednisolone groups were reasonably matched at baseline. Ten out of 24 participants in the dexamethasone group and 6 out of 16 participants in the prednisolone group achieved the trial authors' primary outcome, remission at the end of one year, a difference which was not significant (RR 1.11; 95% CI 0.50 to 2.45). Seven of 24 participants in the dexamethasone and 8 of 16 participants in the prednisolone group deteriorated. The CSR authors felt this provided moderate-quality evidence that there was no significant difference in improvement in disability after one year. There were also no significant differences between the groups in change in Medical Research Council (MRC) sum score, grip strength, INCAT disability scale, INCAT sensory sum score, or Short Form-36 (SF-36) Health Survey scores. Improvement was somewhat faster in the dexamethasone-treated group. Median time to remission was 20 weeks (95% CI 12.4 to 27.6) in the dexamethasone group in comparison to 39 weeks (95% CI 29.9 to 48.1) in the prednisolone group (P = 0.057). Adverse effects including diabetes mellitus, hypertension, weight gain, and osteopenia were not significantly different between oral prednisolone and monthly dexamethasone with the exception of sleeplessness and cushingoid facies, which were significantly more common in the prednisolone group. One participant in the dexamethasone group developed acute glaucoma after one cycle and stopped treatment.

Plasma exchange

The updated CSR of plasma exchange (Mehndiratta 2015) identified two RCTs. The trials compared the short-term efficacy (at 3 weeks and 4 weeks) of plasma exchange and sham exchange (Dyck 1986; Hahn 1996). Neither trial addressed the one-year disability outcomes preferred for this overview. The review authors judged both studies to be high quality and at low risk of bias, but the sample sizes were small. Mehndiratta 2015 did not include a RCT of plasma exchange for CIDP in participants with IgG and IgA paraproteinaemic neuropathy, but the updated CSR of treatments for paraproteinaemic neuropathy (Stork 2015) includes this trial.

Plasma exchange versus sham exchange

Dyck 1986 was a parallel-group trial with 29 participants that compared twice-weekly plasma exchange administered for three weeks to a similar course of sham exchange. Hahn 1996a was a multicentre cross-over trial that compared 10 plasma exchanges with a similar number of sham exchanges delivered over four weeks, with an intended washout period of five weeks. Fifteen participants completed the trial. The outcome measures were disability associated. Change in impairment was measured with the NIS after three weeks in Dyck 1986 and after four weeks in Hahn 1996a. Only Hahn 1996a measured change in disability. The scale used was a novel, simple, but unvalidated ad hoc 11-point disability scale. Four weeks after treatment, there was a mean of 2 points (95% CI 0.8 to 3.0 points) more improvement after plasma exchange than after sham exchange. The CSR concluded that, compared to sham exchange, there was moderate-quality evidence that plasma exchange produces short-term improvement in disability and high-quality evidence of improvement in signs of disease as measured by a neurologist (Mehndiratta 2015).

With regard to adverse events, the CSR included non-randomised evidence and concluded that plasma exchange causes adverse events in 3% to 17% of participants (Mehndiratta 2015). Most events were mild, such as hypocalcaemia arising from citrate toxicity, and hypotension. In an open follow-up study (Hahn 1996a), one participant had a myocardial infarction while connected to the cell separator; the relationship to the procedure was uncertain. The CSR also discussed costs and noted that, although costly, plasma exchange is less expensive than IVIg in most countries. The CSR also noted that an expert panel of the European Federation of Neurological Societies (EFNS) and Peripheral Nerve Society (PNS) gave its highest level of recommendation to the statement that if IVIg and corticosteroids are ineffective, plasma exchange should be considered for treating CIDP (Van den Bergh 2010).

Dyck 1991, which was a trial of plasma exchange versus sham exchange in IgG and IgA paraproteinaemic neuropathy, reported a statistically significant improvement in the weakness component of the NIS, but the updated CSR of paraproteinaemic neuropathy treatments considered this evidence to be of low quality (Stork 2015).

Intravenous immunoglobulin

The Eftimov 2013 review of IVIg treatment identified eight RCTs with a total of 332 participants (Vermeulen 1993; Dyck 1994; Hahn 1996; Thompson 1996; Mendell 2001; Hughes 2001; Hughes 2008; Nobile-Orazio 2012). Five studies compared IVIg with placebo, one study compared IVIg with plasma exchange (Dyck 1994), and two studies compared IVIg with corticosteroids (Hughes 2001; Nobile-Orazio 2012). We identified another trial, which was completed but published only in abstract form, that compared IVIg with corticosteroids (Camdessanché 2014). The primary outcome in these studies was clinically significant improvement in disability (as determined and defined by the trial authors) within six weeks of onset of treatment.

Intravenous immunoglobulin versus placebo

Three of the five RCTs comparing IVIg with placebo had a parallel-group design (Vermeulen 1993; Mendell 2001; Hughes 2008), and two had a cross-over design (Hahn 1996; Thompson 1996). Each trial used a total dose of 2 g/kg IVIg administered over two days (Mendell 2001), two to four days (Hughes 2008), or five days (Vermeulen 1993; Hahn 1996; Thompson 1996). In one trial, a maintenance dose of 1 g/kg every three weeks followed a loading dose of 2 g/kg (Hughes 2008). Each study used different outcome measures. The largest study was a randomised, response-conditional cross-over design trial with 117 participants (Hughes 2008). Participants in Hughes 2008 who did not achieve improvement with the randomly-allocated treatment after six weeks received the alternate treatment. After 24 weeks, only participants who improved were rerandomised for an extension period of another 24 weeks. The CSR included the first treatment period because the sample entering the extension phase was biased in favour of treatment response (Eftimov 2013).

For the primary outcome, five RCTs summarising the results of 235 participants provided data (Vermeulen 1993; Hahn 1996; Thompson 1996; Mendell 2001; Hughes 2008). The CSR assessed outcomes on disability scales used in the trials (which differed between trials) at time points of 14 days (Thompson 1996), 16 to 21 days (Vermeulen 1993), 28 days (Hahn 1996), and 42 days (Mendell 2001; Hughes 2008). The CSR authors obtained 42-day data for Hughes 2008. According to high-quality evidence, at the end of the trials more participants had improved after IVIg (78 out of 141; 53%) than after placebo (30 out of 28; 23%), with an RR of 2.40 (95% CI 1.72 to 3.36). The number needed to treat for an additional beneficial outcome was 3.03 (95% CI 2.33 to 4.55).

Only one trial had a longer follow-up; this trial assessed disability in the 117 participants on the adjusted INCAT disability score at 24 weeks (Hughes 2008). Mean improvement from baseline disability was 1.1 (SD 1.8) with IVIg and 0.3 (SD 1.3) with placebo; which was a mean difference of 0.8 (95% CI 0.23 to 1.37). In an alternative analysis, 45 of the 58 participants assigned to placebo did not improve one disability grade at 24 weeks and were switched to IVIg. By contrast, fewer participants (23 of 59) assigned to IVIg did not respond and were switched to placebo (RR 0.50, 95% CI 0.35 to 0.71).

Adverse events, such as headache, nausea, chills, and fever, were more common with IVIg than with placebo in the trials included in the CSR. According to evidence that the CSR authors did not grade, but which we graded for this overview as of high quality, a higher proportion of people experienced adverse effects with IVIg (82 out of 167; 49%) than with placebo (25 out of 141; 18%), which produced a RR of 2.62 (95% CI 1.81 to 3.78). The number needed to treat for an additional harmful outcome (any adverse event) with IVIg was 3.3 (95% CI 2.56 to 4.76). According to evidence that the CSR assessed as high quality, but which we consider moderate quality because of imprecision (N = 315), the risk of serious adverse events was 7% with IVIg and 8% with placebo (RR 0.82, 95% CI 0.36 to 1.87) (Vermeulen 1993; Mendell 2001; Hughes 2008).

Intravenous immunoglobulin versus corticosteroids

One cross-over trial compared IVIg with prednisolone (Hughes 2001). The CSR authors considered the first treatment period only and did not grade the quality of the evidence, although they considered that the trial had a low risk of bias. At four weeks, nine of 16 participants who received IVIg and eight of 13 participants who received prednisolone improved by one point on the INCAT disability scale. The RR was 0.91 (95% CI 0.50 to 1.68), in favour of IVIg but with CIs that included effects in either direction. There were also no clear differences in any other efficacy outcomes measured, including the modified Rankin disability score and MRC sum score. Serious adverse events occurred in one IVIg-treated and two prednisolone-treated participants; the result favoured IVIg but CIs included the possibility of little or no difference between the groups (RR 0.45, 95% CI 0.04 to 4.69).

One parallel-group, blinded trial compared IVIg 2 g/kg with intravenous methylprednisolone 2 g, each given every four weeks for 24 weeks (Nobile-Orazio 2012). The CSR authors considered that this trial provided high-quality evidence. The trialists' own primary outcome was discontinuation of the randomised medication, which occurred in three of 24 participants (13%) in the IVIg group and 11 of 21 participants (52%) in the intravenous methylprednisolone group, which represented a significant difference in favour of IVIg (RR 0.54, 95% CI 0.34 to 0.87). However, according to its protocol, the preselected primary outcome in the CSR was improvement after two weeks of one grade or more on the scale used by the trial authors, in this case the Overall Neuropathy Limitations Scale (ONLS). This outcome occurred in five out of 24 participants who received IVIg and three out of 21 participants who received intravenous methylprednisolone; the result was imprecise and CI allowed for an effect in favour of IVIg and little or no difference (RR 1.46, 95% CI 0.4 to 5.38). The CSR also found little or no difference in mean changes in disability or strength after two weeks. Conclusions about longer-term outcomes were confounded by the switching of non-responders to the alternative treatment. Six months after stopping treatment, relapse had occurred in none of the 10 participants who had responded to intravenous methylprednisolone and eight of 21 participants (38%) who had responded to IVIg, which was a statistically significant difference (P = 0.032, Fisher's exact test). Serious adverse events occurred in two of the 24 participants who received IVIg and none of the 21 participants who received intravenous methylprednisolone.

One open randomised trial compared IVIg, 2 g/kg monthly for six months, with a course of oral prednisone, 0.8 mg/kg daily tapered over six months (Camdessanché 2014). The trial results were published only in abstract form, and thus were not included in the Eftimov 2013 CSR. After three months, improvement by 1 INCAT grade occurred in 14 of 18 participants who received IVIg and eight of 17 participants who received prednisone (RR 1.65, 95% CI 0.94 to 2.90). Serious adverse events occurred in three participants who received IVIg and no participants who received prednisone (RR 6.63, 95% CI 0.37 to 199.59).

Intravenous immunoglobulin versus plasma exchange

One trial compared IVIg with plasma exchange using an observer-blind, cross-over design (Dyck 1994). Plasma exchange was performed twice weekly for three weeks and then weekly for three weeks. Participants received IVIg once weekly at 0.4 g/kg for three weeks and then 0.2 g/kg weekly for three weeks. The trial randomised 20 participants; one withdrew, and of the 19 who took part, 13 completed the IVIg and plasma exchange periods, four completed only the plasma exchange period, and two completed only the IVIg period. There were no disability outcomes and no long-term assessments. Unfortunately, neither the analysis nor the reporting of the study results were ideal because the trial authors primarily contrasted within-period changes (values at the end of each period minus those at the start), an approach that has been criticised because it is not the most statistically powerful way to estimate treatment effects. Here, such comparisons were not statistically significant; there were similar, large improvements from baseline in the NIS with both treatments after six weeks: mean (SD) 38.3 points (34.6) after plasma exchange and mean 36.1 points (32.0) after IVIg. The standardised mean difference between the two treatments was not significant, -0.06 points (95% CI -0.76 to 0.63). The small size of this difference and wide CI suggest that the differences between the two treatments would still not have been statistically significant had a more statistically powerful analysis been used. Another concern about this study is that there were many dropouts, which might have resulted in bias. Furthermore, these analyses may have been biased by the differences at baseline between the participants who took part in each treatment period. The authors of the Eftimov 2013 CSR considered that this trial provided moderate-quality evidence of no significant difference in short-term efficacy between the two treatments.

In the plasma exchange period of this study, “a few” participants required indwelling venous catheters. Minor side-effects such as light headedness, nausea, and rash were “quite common”. No serious complications were recorded during the IVIg treatment periods. Neither we nor the Eftimov 2013 CSR authors are able to comment on the quality of the evidence for the relative frequency of adverse events, because of lack of information.

Azathioprine

There has only been one randomised trial of azathioprine (Dyck 1985). This open-label, parallel-group trial in adults had a high risk of bias. It compared nine months' treatment with a combination of azathioprine 2 mg/kg and prednisone with prednisone alone. Both groups started at 120 mg prednisone every other day, tapered over nine months. Follow-up data were available for 13 of 14 participants in the azathioprine and prednisone group and 10 of 13 participants in the prednisone alone group. The trial authors did not collect measures of disability desired for the CSR (Mahdi-Rogers 2013) and this overview. After nine months, there was a median improvement of 29 points on the Mayo Clinic NIS (range 49 points worse to 84 points better) in the participants who received azathioprine and prednisone, compared with a worsening of 30 points (range 20 points worse to 104 points better) in the prednisone alone group. This difference was not statistically significant, nor were the changes in any of the other clinical measures of impairment or nerve conduction collected by the authors statistically significant. The CSR authors did not grade the evidence quality but we consider it to be very low because of imprecision, a single small study, and lack of blinding.

Methotrexate

One parallel-group trial with a low risk of bias tested the efficacy of low-dose oral methotrexate, a well-tolerated immunosuppressant often used in rheumatoid arthritis (RMC 2009). It randomised 60 adults with CIDP with or without paraprotein (but not anti-myelin-associated-glycoprotein antibodies) to methotrexate (7.5 mg weekly for four weeks, then 10 mg weekly for four weeks, then 15 mg weekly for 32 weeks) or placebo. Both groups received folic acid 5 mg twice weekly as is usually coadministered with methotrexate to prevent mouth ulcers and gastrointestinal side-effects. The primary outcome for the Mahdi-Rogers 2013 CSR and this overview, change in disability after one year, was not available because follow-up ended after 40 weeks. All participants were required to have been receiving corticosteroids, IVIg, or both at the start of the trial. After 16 weeks, the dose of IVIg or corticosteroids was reduced by 20% of the starting dose every four weeks. The trial used the ONLS to measure disability (Graham 2006), which is very similar to the INCAT scale. If participants worsened by one grade, the original IVIg or corticosteroid dose was restarted. The primary outcome was the reduction in corticosteroid or IVIg dose in weeks 37 to 40 compared with weeks one to four. Response was defined as reduction of corticosteroid or IVIg dose by more than 20%. Fourteen of 27 participants (52%) were responders in the methotrexate group and 14 of 32 were responders in the placebo group (44%), adjusted odds ratio 1.21 (95% CI 0.40 to 3.70). The CSR authors graded this as low-quality evidence that methotrexate did not allow more participants to reduce their corticosteroid or IVIg dose by 20% than did placebo.

The closest outcome measure to the primary outcome for the CSR and this overview was change in disability after 40 weeks. This was measured in two ways and the results were not significant with either. The first method compared the median changes from baseline in the ONLS; these were similar in the methotrexate group 0 (interquartile range (IQR) -1 to 0) and the placebo group 0 (IQR -0.75 to 0). The second method compared the mean (SD) changes from baseline of another disability measure, the Amsterdam Linear Disability score, in which the change in the methotrexate group was -0.66 (4.25) and in the placebo group -0.48 (2.40). The mean change from the baseline of the Amsterdam Linear Disability score of the methotrexate group was -0.47 points (95% CI -3.62 to 1.87) less than that of the placebo group, with adjustment for baseline

score, baseline IVIg or corticosteroid dose per week per kg, and age. These changes in disability were not significant and in any case might have been affected by alterations in the corticosteroid or IVIg doses required by the protocol.

Serious adverse events occurred in three participants in the methotrexate group and one participant in the placebo group, RR 3.56 (95 % CI 0.39 to 32.23).

Interferon beta-1a

There have been two RCTs of interferon beta-1a (IFN beta-1a). Hadden 1999 performed a placebo-controlled cross-over trial in treatment-resistant CIDP with treatment periods of only 12 weeks and a four-week washout period. The dose was low: IFN beta-1a 11 µg thrice weekly for two weeks then 22 µg thrice weekly for 10 weeks. The primary outcome for the CSR and this overview was not available, but change in disability 12 weeks after start of treatment was reported. The median within-period improvement in the Guy's Neurological Disability Scale (similar to the INCAT scale) was very similar in the two treatment periods, 0.5 grades (IQR 1.8 grades better to 0 grade change) in the IFN beta-1a treatment period and 0.5 grades (IQR 1.8 grades better to 1.0 grade worse) in the placebo treatment period. As noted above, comparison of within-period changes between treatment groups is not an ideal method of analysis for cross-over trials. Nonetheless the fact that these changes are so similar in the two treatment groups suggests that a more statistically powerful approach would have been unlikely to yield significant results. There were no serious adverse events during either treatment period.

Hughes 2010 conducted a placebo-controlled, parallel group trial of intramuscular IFN beta-1a or matching placebo given in one of four doses: 30 µg once weekly, 60 µg once weekly, 30 µg twice weekly, or 60 µg twice weekly for 32 weeks. This trial used the Overall Disability Sum Score (ODSS), which is almost identical to the ONLS (Graham 2006). After 16 weeks, IVIg was stopped and then restarted if the participant worsened by 1 point on the ODSS and 2 points on the MRC sum score. The trial authors' primary outcome was the total IVIg dose administered in weeks 16 to 32. This was not significantly different between all the IFN beta-1a groups combined (1.20 g/kg) and the placebo group (1.34 g/kg) (P = 0.75). The CSR authors concluded that Hughes 2010 provided moderate-quality evidence of no significant difference between IFN beta-1a and placebo in the risk of not restarting IVIg after the withdrawal phase (47% in both groups). There was high-quality evidence that serious adverse events were not significantly more common with IFN beta-1a, although there were adverse events in four participants in the IFN beta-1a group and none in the placebo group, RR 4.50 (95 % CI 0.25 to 80.05). The outcomes desired for the CSR and this overview were not available, except for serious adverse events.

Other pharmacological agents and immunosuppressive regimens

There have been no RCTs of other immunosuppressive or immunomodulatory agents. A parallel-group trial of oral fingolimod 0.5 mg daily versus placebo started in 2013, but participant recruitment was halted in 2016 because of futility (FORCIDP 2013; Hartung 2014).

Treatment for fatigue

A published CSR for assessing treatment for fatigue in peripheral neuropathy identified no randomised trials in people with CIDP (White 2014). Neither the review nor our searches for this overview identified any RCTs of interventions for fatigue in CIDP.

Treatment for pain

Our search did not reveal any systematic reviews or RCTs of treatment for pain in CIDP, but there have been multiple high-quality trials and several CSRs of treatment for neuropathic pain caused by polyneuropathy and herpes zoster (postherpetic neuralgia) (Hempenstall 2005).

Discussion

Summary of main results

Corticosteroids

The conclusions that can be drawn about the efficacy of corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are limited because they depend on only two trials (Hughes 2015). It is uncertain whether daily oral prednisone produces improvement in impairment compared to no treatment, because the evidence is very low quality. According to moderate-quality evidence from the other trial, high-dose monthly oral dexamethasone for six months probably does not differ significantly in efficacy from daily oral prednisolone. Both treatments caused short-term side-effects, but, also according to moderate-quality evidence, sleeplessness and moon-shaped face were probably less common with monthly dexamethasone. The paucity of evidence contrasts with the extensive use of corticosteroids in practice and their recommendation as a primary treatment option for CIDP in international guidelines (Van den Bergh 2010).

Plasma exchange versus sham exchange

Two trials of plasma exchange compared with sham exchange for CIDP provided moderate-quality evidence of more improvement in disability, and high-quality evidence of more improvement in impairment with plasma exchange (Mehndiratta 2015). The improvements were large and clinically important. Serious adverse events occurred in two of 52 randomised participants. The review authors did not comment on the quality of the evidence about adverse events, but we consider the evidence about adverse events to be of very low quality because of unclear reporting.

In paraproteinaemic neuropathy, one trial provided some evidence of more improvement in impairment with plasma exchange than sham exchange (Dyck 1991). The Stork 2015 Cochrane Systematic Review (CSR) did not grade the evidence for benefit but we consider the evidence of low quality because of serious imprecision. There were no data

about adverse events for the trial (Dyck 1991).

Intravenous immunoglobulin versus placebo

In the Eftimov 2013 CSR of intravenous immunoglobulin (IVIg) in CIDP, five trials provided evidence that more participants had short-term improvement in disability after IVIg (44%) than after placebo (18%) (risk ratio (RR) 2.40, 95% confidence interval (CI) 1.72 to 3.36). Adverse events were more common with IVIg than with placebo. Serious adverse events were probably no more common with IVIg than with placebo. One trial had a 24-week extension phase in which responders were rerandomised to IVIg or placebo (Hughes 2008). Relapses were less common in the IVIg recipients: specifically, no relapse occurred in 37/43 (86%) participants in the IVIg group compared with 16/31 (52%) in the placebo group (absolute risk reduction 34% (95% CI 14 to 55%) and the number needed to treat for an additional beneficial outcome was 2.94 (95% CI 1.82 to 7.13). The Eftimov 2013 CSR excluded these results because of potential bias of the extension period enrichment design that would be expected to exaggerate the efficacy of IVIg.

Azathioprine

It is uncertain whether the addition of azathioprine (2 mg/kg) to prednisone improves impairment, as the quality of the evidence is very low (1 trial, 27 participants) (Dyck 1985). The trial did not report adverse events.

Methotrexate

According to low-quality evidence from one trial, there may be little or no difference between methotrexate and placebo in the change in disability as measured with either the Overall Neuropathy Limitations Scale (ONLS) or the Amsterdam Linear Disability score after 40 weeks' treatment (RMC 2009). There were more serious adverse events with methotrexate than with placebo.

Interferon beta-1a

One trial of interferon beta-1a (IFN beta-1a) showed little or no benefit after 12 weeks. According to evidence judged to be of moderate quality by the Mahdi-Rogers 2013 CSR, the only other trial of IFN beta-1a found little or no benefit from IFN beta-1a after 32 weeks. This trial did not identify more serious adverse events with IFN beta-1a than with placebo, evidence which the review authors considered high quality but which we considered only moderate quality because it lacked precision.

Direct comparisons of corticosteroids, plasma exchange and intravenous immunoglobulin

Intravenous immunoglobulin versus corticosteroids

The evidence directly comparing corticosteroids and IVIg depends on three RCTs, of which one has not been published in full nor incorporated in a CSR (Camdessanché 2014). One blinded cross-over trial comparing IVIg with oral prednisolone had only 32 participants. It did not show a significant difference between the treatments in either six-week improvement of disability or occurrence of serious adverse events (Hughes 2001). A parallel-group, blinded, six-month trial comparing IVIg with intravenous methylprednisolone did not show significant differences in disability after two weeks, but did show that significantly more participants responded to IVIg in the short term (Nobile-Orazio 2012). According to unpublished information provided by the trial authors, an open, six-month, parallel-group trial comparing IVIg with oral prednisone did not show clear differences in disability after three months (Camdessanché 2014). However, the CIs include both no difference between the treatments and a relevant difference. Although Camdessanché 2014 suggested that treatment response was more likely with IVIg than intravenous methylprednisolone, the other two studies did not support this conclusion. All three studies were small. The discordance of outcomes and treatment intervals in these three RCTs prevented us combining their results in a meta-analysis. Thus, the low numbers of participants in these somewhat heterogeneous trials comparing IVIg with corticosteroids make it impossible to draw confident conclusions about which intervention, if either, is superior. For the same reason, it is unclear whether the more frequent occurrence of serious adverse events with IVIg than with corticosteroids in each of these trials represents a real difference or is coincidental (1/30 with IVIg and 0/27 with prednisolone in Hughes 2001, 2/24 with IVIg and 0/21 with intravenous methylprednisolone in Nobile-Orazio 2012, and 3/18 with IVIg and 0/17 with prednisone in Camdessanché 2014). A meta-analysis combining these results gives a RR of 4.56 (95% CI 0.82 to 25.39), indicating more adverse events with IVIg than with corticosteroids but with very serious imprecision. The trials did not last long enough to detect the known serious side-effects of long-term corticosteroid treatment.

A retrospective non-randomised comparison of two groups of people with CIDP, one group of 36 who were dependent on maintenance treatment and one group of 34 who were able to withdraw treatment, found that IVIg was more often effective than corticosteroids but successful withdrawal from treatment was more common after corticosteroids than after IVIg (Rabin 2014). This trial also identified multifocal deficit and a longer delay in starting treatment as factors associated with treatment dependence. More prospective, preferably randomised, studies are needed to confirm these observations.

Intravenous immunoglobulin versus plasma exchange

A single, small cross-over trial showed no significant difference in change in impairment after six weeks between IVIg and plasma exchange (Dyck 1994). The CSR assessed this as moderate-quality evidence (Eftimov 2013).

Corticosteroids versus plasma exchange

There have been no direct comparisons of corticosteroids with plasma exchange.

Indirect comparisons of corticosteroids, plasma exchange and intravenous immunoglobulin

Indirect comparisons of corticosteroids, IVIg, and plasma exchange with network analysis were not possible because of differing outcome measures and times of data collection between trials. Limited conclusions about the comparison of the short-term efficacy of corticosteroids versus IVIg, and IVIg versus plasma exchange can be drawn from the small direct comparative trials cited above. With regard to the comparison of corticosteroids and plasma exchange, there is some relevant information: in the Dyck 1982 trial there was a median improvement of 5 NIS points after 12 weeks of prednisone treatment, compared with a median worsening of 2 NIS points with no treatment, and in the Mehndiratta 2015 CSR meta-analysis of the two plasma exchange trials, a mean improvement in NIS of 30.6 points (95% CI 44.72 to 16.49) more after three or four weeks of plasma exchange than after sham exchange (Mehndiratta 2015). Although the differences in treatment times and participant characteristics precluded formal network analysis, the 24-point greater improvement with plasma exchange than with corticosteroids could suggest that plasma exchange has greater short-term efficacy.

Other immunosuppressive or immunomodulatory regimens

Neither the Mahdi-Rogers 2013 CSR, nor the search conducted for this overview identified any completed RCTs of other immunosuppressive or immunomodulatory agents or regimens other than those described above. The CSR described observational studies of other immunosuppressive regimes in its discussion. These included alemtuzumab, cyclophosphamide, ciclosporin, interferon alfa, mycophenolate, natalizumab, rituximab, tacrolimus, and bone marrow stem cell transplantation. None of the studies was so convincing as to avoid the need for RCTs to establish the balance between benefit and harm for these regimens. Reports that treatment with some of these agents for other conditions has been associated with the onset of inflammatory neuropathy, as noted by the CSR, are concerning. A parallel-group trial of oral immunosuppressant drug fingolimod 0.5 mg daily started in 2013, but participant recruitment was halted in 2016 because of futility (FORCIDP 2013; Hartung 2014). Despite the absence of evidence from RCTs, immunosuppressant regimes, such as azathioprine, mycophenolate, and cyclophosphamide, are often used in clinical practice in people with CIDP who are either resistant to first-line treatments, or in whom side-effects, cost, or inconvenience of first-line treatments become problematic (Cocito 2010).

Adverse events

All the treatments considered in this overview carry the risk of side-effects, which the available reviews of predominantly short-term trials have not captured adequately. The 12-week trial of oral prednisolone did not give details of adverse events. Monthly dexamethasone treatment for six months caused short-term side-effects with a similar frequency to daily oral prednisolone, but sleeplessness and moon facies were less common with dexamethasone (moderate-quality evidence). Corticosteroids are known from observational studies to carry a long-term risk of serious side-effects.

IVIg caused significantly more adverse events than placebo. Serious adverse events were not significantly more common; however, the sample size was small for quantification of serious adverse events. Serious side-effects have occurred in observational studies.

Serious adverse events occurred in the plasma exchange versus sham exchange trials. Observational studies have reported adverse events related to difficulty with venous access, use of citrate, and haemodynamic changes.

The trial of azathioprine did not report adverse events. In the included review, serious adverse events were not more frequent with IFN beta-1a or methotrexate than with placebo. Serious side-effects have occurred, especially with azathioprine and methotrexate, in observational studies.

Factors affecting the choice of treatment

Despite the lack of high-quality evidence for the efficacy of corticosteroids from randomised trials, use of oral corticosteroid regimens will continue because of favourable empirical clinical effectiveness, global availability, familiarity of neurologists with their use, convenience of administration, and low cost. Against this, the serious and potentially costly adverse effects of long-term use must be considered.

There is more published evidence for the efficacy of IVIg than for corticosteroids or plasma exchange. IVIg is both less available and less convenient than corticosteroids, but more available and convenient than plasma exchange. IVIg has a different adverse effect profile to corticosteroids, but is not free of adverse events. In the non-randomised literature, mild transient adverse effects occurred in 1% to 15% of IVIg infusions (Duhem 1994; Stiehm 1996). In a parallel-group RCT involving 27 participants, there was no significant difference in efficacy or side-effect profile of two different brands of IVIg (Kuitwaard 2010). In a retrospective review of 244 people with neurological conditions, of whom the majority were older than 60 years, the rate of adverse effects with IVIg was 35% (Lozeron 2016). Most of these adverse effects were transient hypertension and headache, but acute renal dysfunction and venous thrombosis occurred in 2%. Other severe side-effects, including generalised erythematous skin reactions (Hurelbrink 2013), anaphylactic shock, haemolytic anaemia, and stroke seem to be uncommon, occurring in fewer than 0.5% of more than 26,000 infusions in a post-marketing clinical pharmacovigilance study (Martin 2000). One of the disadvantages of IVIg is the inconvenience and expense of attending hospital for the infusions, which last for several hours. This is increasingly mitigated by at-home administration where this is possible (Katzberg 2013).

Subcutaneous immunoglobulin could be a more convenient alternative to IVIg if it were as effective, particularly as the treatments can be administered at home. The Markvardsen 2013 RCT, involving 29 participants, has not yet been included in a CSR, but it showed that subcutaneous immunoglobulin produced more improvement in strength than placebo. Twenty of 29 participants said that they preferred subcutaneous to intravenous immunoglobulin. A recent meta-analysis concluded that subcutaneous and intravenous immunoglobulin are equally effective in CIDP and in

multifocal motor neuropathy (Racosta 2016). The ongoing Van Schaik 2016 RCT is also investigating the efficacy of subcutaneous immunoglobulin and the next updates of Eftimov 2013 and this overview will include this trial.

The fact that there is more evidence for the efficacy of IVIg mainly reflects that more studies have been conducted. This is through industry support and the necessity for licensing and does not mean that IVIg is more effective than other treatments. As noted above, the trials comparing IVIg with corticosteroids did not show a significant difference in short-term efficacy.

There is probably little or no difference in short-term efficacy between plasma exchange and IVIg. Inconvenience and discomfort, the requirement for hospital attendance and specially trained staff, and the risk of side-effects limit the use of plasma exchange. In a series of 381 plasma exchange procedures for various indications, complications, usually from the use of a central venous catheter, occurred in 17% of 381 procedures. These events included two deaths, one from arterial haemorrhage caused by the insertion of a central venous catheter, and one from the underlying disease (Couriel 1994). In a larger series, complications occurred in 3.9% of 17,940 procedures on 3583 people and included citrate toxicity (3%), vasovagal reactions, vascular access complications, cardiac arrhythmia, haemolysis, hepatitis B, and fresh frozen plasma reactions, but no treatment-related deaths (Kiprov 2001).

Overall completeness and applicability of evidence

The evidence included in this overview covers all the randomised trials of treatments for CIDP that we found, except for six trials that are awaiting incorporation into individual CSRs. One trial of lipoic acid has been completed according to the ClinicalTrials.gov entry but the contact has not answered our request for the results (NCT00962429). Another trial, of 3,4-diaminopyridine, a drug hoped to improve conduction in partly demyelinated nerve fibres, showed no significant benefit on any measure of impairment. This trial has not been included in any CSR because it has not fallen within their inclusion criteria, and a title will be registered for it and similar agents. The study had a blinded cross-over design, included 34 stable participants and used only four days of treatment (Russell 1995). There have been no other trials of this drug in CIDP, but trials of a similar drug, 4-aminopyridine, showed an improvement in walking speed in multiple sclerosis and resulted in its registration for that indication by the Food and Drugs Administration in the USA (Goodman 2009). In a third trial, Hu 2009 tested Guilong Tongluo Capsule in 60 people with CIDP. Half of the participants received the capsule and prednisone, and half of them received prednisone alone. After three months, the "total effective rate" on a variety of measures was 90.0% (27/30) with Guilong Tongluo Capsule and 70.0% (21/30) without the intervention, which is not statistically significant (Fisher's exact test P = 0.104), despite the trial authors' claim to the contrary.

Corticosteroids

The conclusion of the Hughes 2015 CSR that the one randomised trial of oral corticosteroids did not show a statistically significant benefit over no treatment appears to be at odds with clinical experience. However, the quality of the evidence from the randomised study was very low; with a high risk of bias and imprecise results that allowed for large effects in favour of corticosteroids and little or no difference. Following current Cochrane practice, which reports findings in terms of the quality of evidence rather than their statistical significance, we have stated the effect of corticosteroids in this trial to be uncertain because of the very low-quality evidence. In the absence of more evidence from RCTs, the Hughes 2015 CSR considered the evidence from observational studies. These uniformly reported the apparent efficacy of corticosteroids. The largest and most helpful, albeit retrospective, study, included 136 participants from Italy treated with corticosteroids as first-line therapy; 51% responded with a one or more point improvement in the Rankin disability score, and 12.5% had adverse effects (five had diabetes mellitus, four hypertension, three osteoporosis, three duodenal ulcer, two psychosis, and one obesity) (Cocito 2010). Fourteen participants who had previously been treated with IVIg were switched to corticosteroids, and six participants (43%) responded. This very low-quality evidence suggests that corticosteroids can induce at least short-term improvement in about half of people with CIDP. The Cocito 2010 study also documented the improvement of some people on corticosteroids after switching from IVIg.

Intravenous immunoglobulin and plasma exchange

There is at least moderate-quality evidence included in this overview supporting the short-term efficacy of IVIg and plasma exchange, but the evidence is limited by the small numbers of trials, the low numbers of participants and by the short duration of follow-up, which was in many cases limited to four to six weeks. We considered evidence from one trial suggesting efficacy of IVIg for as long as 24 weeks to be potentially biased by exclusion of non-responders from randomisation. Clinical experience suggests that benefit from regular IVIg or plasma exchange treatments can last beyond six months, although trials have not so far investigated longer-term effects. Most trials reported adverse events; however, longer-term follow-up is also necessary to capture adverse events adequately and we have indicated observational studies reporting these.

Azathioprine, methotrexate, and interferon beta-1a

Based on evidence from single trials, it is uncertain whether azathioprine is of benefit in CIDP, and methotrexate may have no clear benefit. Two trials of IFN beta-1a for CIDP provided moderate quality evidence of no significant benefit. This evidence is limited by the small size of the trials and the low doses used: only 2.0 mg/kg daily of azathioprine (maximum dose 2.5 mg/kg daily) (Dyck 1985) and 15 mg weekly of methotrexate (RMC 2009). The doses of IFN beta-1a ranged from very low, 30 µg once weekly, to very high, 60 µg twice weekly (Hughes 2010).

The trial of azathioprine only lasted for nine months, whereas in a similar trial in myasthenia gravis a treatment effect did not become evident until after 12 months (Palace 1998), so it would be premature to draw conclusions about the efficacy of azathioprine from this trial alone. The CSR summarised results from published case series in which 28 of

88, about one third of participants, were reported to have benefited (Mahdi-Rogers 2013). Thus the quality of the evidence from the trial and from observational studies is very low and inadequate to establish whether azathioprine is beneficial in CIDP. Furthermore, although the trial did not report side-effects, in observational studies azathioprine is known to cause nausea, vomiting, diarrhoea, and allergic reactions, including rash, which prevent its continuation in about 10% of people. Azathioprine also causes leucopenia, altered liver function, and increased susceptibility to infection (Confavreux 1996; Kissel 1986). There is a theoretical risk of neoplasia but a large retrospective cohort study of immunosuppressive agents in autoimmune ocular disease did not show an actual increased incidence in people treated with antimetabolites such as azathioprine, methotrexate, and mycophenolate mofetil after 17,316 person-years (Kempen 2009).

The evidence concerning methotrexate was limited by the unexpectedly high proportion of responders in the placebo group and the subjective component in the dose adjustment on which the primary outcome depended. There is little information about benefit from observational studies: the CSR identified published reports of benefit in about one-third of people (8 of 23) with CIDP who were treated with the drug (Mahdi-Rogers 2013). Side-effects of methotrexate are well recognised. However, in a retrospective review of 248 people with rheumatoid arthritis on a mean dose of methotrexate 12.6 mg at the last visit, only 0.8% stopped taking methotrexate because of laboratory abnormalities and 10% because of side-effects (Yazici 2005).

Neither trial of IFN beta-1a included in the CSR showed clear benefit. Although apparent benefit was reported in 15 of 34 participants in case reports and case series identified in the CSR, such evidence is highly susceptible to reporting bias and this method of treatment has not been pursued. IFNb-1a often causes minor alterations of liver function and white cell counts and, upon subcutaneous administration, skin reactions, but serious side-effects are rare (Rice 2001).

Treatment for fatigue

Our search did not reveal any RCTs of treatment for fatigue that included participants with CIDP.

Treatment for pain

Although many trials and some systematic reviews of treatment for painful neuropathy exist, our search did not reveal any trials that randomised participants with CIDP. It is possible but not known that people with CIDP respond to similar agents, and these are often used in practice.

Paraproteinaemic neuropathies

it is uncertain whether the evidence summarised here for CIDP can be applied to people who also have a paraprotein. Paraproteins are sometimes associated with CIDP. Paraproteins can be associated with malignant plasma cell dyscrasias but commonly there is no current evidence of neoplasia and the paraprotein is classified as a "monoclonal gammopathy of undetermined significance" (MGUS). At least half of people with IgM paraproteins have associated antibodies to myelin-associated glycoprotein and are therefore classified as not having CIDP. Those with IgG or IgA paraproteins often have a similar clinical course to CIDP without a paraprotein and are classified as having atypical CIDP (Van den Bergh 2010). Limited evidence from one randomised trial described above showed that plasma exchange produced significant short-term benefit compared with sham exchange (Dyck 1991). Randomised trials of corticosteroids or IVIg have not been performed specifically in people with this disease variant, but very small numbers of such people have been participants in some of the trials included in this overview.

The evidence in this overview is based on RCTs involving adults with more or less typical forms of CIDP. Most RCTs excluded children, in whom observational studies suggest that IVIg and corticosteroids are equally likely to be effective (McMillan 2013). Trials also excluded the very old, for whom no separate information is available, and atypical forms of CIDP. Large case series and narrative reviews of the treatment of such people may be informative, but fall outside the scope of this review. Observational studies have reported deterioration of pure motor CIDP with corticosteroids (Donaghy 1994). On this account, corticosteroids are not generally recommended in this atypical variant (Van den Bergh 2010). Ayrignac 2013 reported a series of 22 people with pure sensory CIDP; in 14 of 15 people who received immunotherapy, the treatment was considered effective. Participants in the trials also needed to be without significant comorbidity, so conclusions may not be applicable to people who have coexistent diabetes mellitus, which might be considered a relative contraindication to corticosteroids.

Costs

Economic analyses are difficult to perform and the outcomes vary depending upon the model used, the variables considered, the time over which costs are averaged and the healthcare system in which the treatment is provided. Corticosteroids, especially oral prednisolone and dexamethasone, are inexpensive and these are the cheapest of the three treatments currently recommended by the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guideline by orders of magnitude (Van den Bergh 2010). For much of the global population, these are the only available treatment options. IVIg is the most expensive: one European study calculated the extra cost of IVIg compared with corticosteroids per quality-adjusted life year (QALY) gained as EUR 250,000 (McCrone 2003). A Canadian study estimated the incremental cost per QALY gained of IVIg compared with corticosteroids as CAD 687,287 (approximately USD 535,800) (Blackhouse 2010). By contrast, based on societal willingness-to-pay thresholds, a study in Thailand concluded that IVIg is a cost-effective treatment for corticosteroid-resistant CIDP (Bamrungsawad 2016). Nevertheless, in many countries IVIg is not an affordable option, whereas plasma exchange can be a more available and affordable alternative to corticosteroids. Other immunosuppressants have not been shown to offer significant benefit but if they were shown to be effective, older oral treatments would offer significant cost

benefits, in particular when compared with IVIg.

Quality of the evidence

The methods used in each of the CSRs followed Cochrane standards and fulfilled the desirable attributes in the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) checklist (see Table 1).

We consider the small number of trials and participants to be the major impediment to producing a high-quality review, especially those addressing the long-term disability outcome desired for this overview.

Potential biases in the overview process

The overview process is vulnerable to criticism in that some of the overview authors also authored some of the trials or reviews included in this overview and had consultancies with some of the companies producing the drugs being considered (see Declarations of interest). Where judgments about quality were made, two overview authors who had no commercial conflicts of interest and who were not authors of included CSRs made assessments independently. Additionally, these authors performed an independent selection of reviews and studies for inclusion.

Agreements and disagreements with other studies or reviews

There have been no other formal systematic overviews of treatments for CIDP. Other reviews have quoted the relevant CSRs and reached the same conclusions as this overview, namely that corticosteroids, plasma exchange and IVIg have significant short-term efficacy (Fergusson 2005; Donofrio 2009). One systematic review (Bright 2013) included three trials excluded from our review:

1. A trial of rituximab for anti-myelin-associated glycoprotein-associated antibody demyelinating neuropathy (Dalakas 2009), which is generally considered a different entity from CIDP and which did not fulfil the inclusion criteria for our review.
2. A trial comparing immunoabsorption with IVIg (Zinman 2005), which the Eftimov 2013 review excluded because of low quality related to loss to follow-up of 10 of the 20 participants at six months.
3. A trial of IVIg versus placebo in multifocal motor neuropathy (Léger 2001), which did not fulfil the inclusion criteria for our review.

In addition, Bright 2013 excluded the trials of plasma exchange and did not mention the trials comparing IVIg with corticosteroids. Despite these differences, Bright 2013 reached similar conclusions to ours. An expert panel of the EFNS and PNS considered that the evidence for short-term efficacy of corticosteroids was of moderate quality (Class II in their classification), for IVIg of high quality (Class I), and for plasma exchange of high quality (Class I) (Van den Bergh 2010). Despite the absence of confirmatory trials, the same panel recommended combination treatments or adding an immunosuppressant or immunomodulatory drug for treatment of resistant disease.

Authors' conclusions

Implications for practice

The available reviews provide evidence of variable quality, mostly from short-term trials, about the efficacy of different treatments. It is uncertain from the randomised controlled trial (RCT) evidence whether daily oral prednisone for 12 weeks produces more improvement than no treatment for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). High-dose monthly oral dexamethasone for six months probably does not differ significantly in efficacy from daily oral prednisolone. Use of corticosteroids is widespread, supported by clinical experience and very low-quality evidence from observational studies.

Intravenous immunoglobulin (IVIg) produced more short-term (four-week to six-week) improvement in disability than placebo. There is little or no difference in short-term improvement of disability with IVIg in comparison with intravenous methylprednisolone, and probably little or no difference in comparison with oral prednisolone.

Plasma exchange probably produces more short-term improvement in disability than sham exchange. There is probably little or no difference in short-term improvement in impairment with plasma exchange compared to IVIg.

At the mostly low doses tested, it is uncertain whether azathioprine is effective, as the evidence is very low quality; methotrexate may not be effective; and interferon beta-1a is probably not effective. There are no completed RCTs of other immunosuppressive or immunomodulatory agents.

There is not enough evidence overall, and no high-quality evidence, to make indirect statistical comparisons (across trials) of the relative efficacy of any of the interventions that have been investigated in RCTs. The collection and reporting of adverse events in the performed trials is variable. Furthermore, where adverse events are relatively uncommon and their occurrence too infrequent to pick up in small trials, the data presented for adverse events from these trials cannot be used to influence clinical decisions about the relative safety of one agent over another. Practitioners and people with CIDP should consider well-known adverse effects of the agents from case series and trials in other conditions described in this overview when making a choice of treatment.

A significant number of heterogeneous agents with potential efficacy in CIDP have not been studied in a high-quality RCT. We cannot comment on their efficacy and safety in practice in this overview.

Implications for research

We need further research to compare the risk of side-effects and long-term benefit from the agents which produce short-term benefit. We need to identify genetic, immunological, or other factors which predict individual responses to each of the treatments including the risk of deterioration following their withdrawal. We also need to compare the cost-effectiveness of

these treatments in different healthcare settings. Evidence-based consensus concerning outcome measures and time points would assist comparison of different agents and trials. Testing larger doses of azathioprine or methotrexate or some of the many other available immunomodulatory agents as initial, secondary, or combination treatments would be worthwhile. Research should also include treatments for fatigue and pain in CIDP and investigation of the role of psychological and social factors in causing disability.

Acknowledgements

We have quoted, sometimes verbatim, from the five Cochrane Systematic Reviews on which this overview is based (Eftimov 2013; Hughes 2015; Mahdi-Rogers 2013; Mahdi-Rogers 2013; Stork 2015), and thank the review authors for allowing this.

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The Cochrane Neuromuscular Information Specialist, Angela Gunn, carried out the literature searches.

Contributions of authors

ALO and CHC prepared the first draft of this update. All authors commented on and edited the first and subsequent drafts, and approved the final version.

Declarations of interest

ALO receives research grant support from the U.S. National Institutes of Health and Department of Defence; she has no commercial interests.

CHC is a co-author of two papers cited in this overview: a study of plasma exchange in CIDP (Hahn 1996), and a cost-benefit analysis of IVIg in CIDP (Blackhouse 2010).

RACH holds or has held consultancies with companies which manufacture human immunoglobulin: Baxter, CSL Behring, Grifols, LFB, and Octapharma, and with Novartis, which is undertaking a trial of fingolimod in CIDP. RACH is co-author of three CSRs Hughes 2015 (steroids), Mehndiratta 2015 (plasma exchange), Mahdi-Rogers 2013 (other immunomodulatory treatment) incorporated in this overview. RACH was co-ordinator, or steering committee chair, and author of the following trials included in the overview: Hadden 1999, Hughes 2001, Hughes 2010, Hughes 2013, RMC 2009, and Thompson 1996. He is Honorary Member of the Board of GBS CIDP Foundation International and Medical Patron of GBS Support Group UK now called 'gain'. He is a member of the Cochrane Neuromuscular Editorial Board but played no role in the editorial process for this overview.

MPTL was co-author of one of the CSRs included in this overview (Stork 2015). He has received honoraria for consultation from Baxter Pharmaceuticals, CSL Behring and UCB Pharma and travel support grant from Grifols and Baxalta (previously Baxter Phamaceuticals), all manufacturers of IVIG. He was a blinded investigator in the study of Comi et al. 2002. MPTL is a blinded investigator in the CSL Behring PATH studies (ongoing). and was a blinded investigator in the FORCIDP study, closed in 2016 for futility. He is Co-ordinating Editor of Cochrane Neuromuscular but played no role in the editorial process for this overview.

CF holds a consultancy with CSL Behring (for which his institution receives payment). He was formerly the group Statistician in Cochrane Neuromuscular. He played no part in the editorial process of this overview.

IvS was chief investigator of one of the included trials (Van Schaik 2010) and co-author of one of the CSRs included in this overview (Eftimov 2013). He chairs a steering committee for CSL-Behring and received departmental honoraria for serving on scientific advisory boards for CSL-Behring, Baxalta, and UCB. He received speakers fees from CSL-Behring and Kedrion. Departmental research support has be granted by The Netherlands Organisation for Scientific Research, and the Dutch Prinses Beatrix Spierfonds. All lecturing and consulting fees for INS were donated to the Stichting Klinische Neurologie, a local foundation that supports research in the field of neurological disorders. He serves on the editorial board of the Cochrane Neuromuscular Disease Group, is a member of the organising committee of the Inflammatory Neuropathy Consortium (INC), a standing committee of the Peripheral Nerve Society and is a member of the Scientific Board of the Kreuth III meeting on the optimal use of plasma-derived medicinal products, especially coagulation factors and normal immunoglobulins organised under the auspices of the European Directorate for the Quality of Medicines & HealthCare (EDQM).

He played no part in the editorial process for this overview.

Differences between protocol and review

Two authors (ALO and CHC) joined the overview after publication of the protocol.

We were unable to make indirect comparisons between treatments using network meta-analysis because the trials were not suitable for comparison.

Published notes

Additional tables

1 AMSTAR* quality criteria for systematic reviews

1. Was an ‘a priori’ design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest stated?

Footnotes

*AMSTAR: Assessing the Methodological Quality of Systematic Reviews
The answer to all these questions was yes for all the included Cochrane Systematic Reviews wherever the questions were applicable with the following questions. For question 4 the answer was ambiguous since all types of publication were searched and used where the quality criteria for a trial were fulfilled and the criteria adequately reported. Question 9 was only applicable for the interventions for which there was more than one trial of the same intervention (PE, IVIg and IFN beta-1a). Question 10 was not applicable in any of the reviews because there were insufficient trials to create a meaningful funnel plot.

2 Characteristics of excluded reviews

Reference	Title	Reason for exclusion
Bright 2013	Therapeutic options for chronic inflammatory demyelinating polyradiculoneuropathy: A systematic review	No pre-determined objective
Cortese 2011	Evidence-based guideline update: Plasmapheresis in neurologic disorders: Report of the Therapeutics and Technology Assessment Subcommittee of the AAN	No pre-determined objective
Donofrio 2009	Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions: report of the AANEM ad hoc committee	No pre-determined objective
Elovaara 2008	EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases	No pre-determined objective
Fergusson 2005	Use of intravenous immunoglobulin for treatment of neurologic conditions: a systematic review	No pre-determined objective Lacks largest IVIg trial
Gaebel 2009; Gaebel 2010	Intravenous immunoglobulin for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review and meta-analysis	No pre-determined objective
Lehmann 2013	Treatment of chronic inflammatory demyelinating polyradiculoneuropathy	Narrative review Quotes CSRs
Patwa 2012	Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the AAN	No pre-determined objective
Stübgen 2013	A review of the use of biological agents for chronic inflammatory demyelinating polyradiculoneuropathy	Narrative review
Van den Bergh 2010	EFNS/PNS guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the EFNS and PNS - First revision	No pre-determined objective Quotes CSR
Vanasse 2013a	Chronic inflammatory demyelinating polyneuropathy (in children)	Narrative review. Quotes CSRs
Buehler 2015	Is there evidence for recommending specific intravenous immunoglobulin formulations? A systematic review of head-to-head randomized controlled trials	No pre-determined objective
Racosta 2016	Subcutaneous vs intravenous immunoglobulin for chronic auto-immune neuropathies: A meta-analysis	No pre-determined objective

Footnotes

AAN: American Academy of Neurology; AANEM: American Academy of Neuromuscular and Electrodiagnostic Medicine; CSR: Cochrane Systematic Review; EFNS: European Federation of Neurological Societies; IVIg: intravenous immunoglobulin; PNS: Peripheral Nerve Society

3 Randomised controlled trials

	Comparison	References
1	**Prednisone** versus supportive treatment alone	Dyck 1982
2	**Azathioprine** and prednisone versus prednisone	Dyck 1985
3	**Plasma exchange** versus sham exchange	Dyck 1986
4	**Plasma exchange** versus sham exchange in neuropathy associated with monoclonal gammopathy of undetermined significance	Dyck 1991
5	**IVIg** versus placebo	Vermeulen 1993
6	**Plasma exchange** versus **IVIg**	Dyck 1994
7	**3,4-diaminopyridine** versus placebo	Russell 1995
8	**Plasma exchange** versus sham exchange	Hahn 1996a
9	**IVIg** versus placebo	Hahn 1996
10	**IVIg** versus placebo	Thompson 1996
11	**Interferon beta-1a** versus placebo	Hadden 1999
12	**IVIg** versus **prednisolone**	Hughes 2001*; McCrone 2003
13	**IVIg** versus placebo	Mendell 2001
14	**IVIg** versus placebo (ICE trial)	Hughes 2008*; Hughes 2009; Merkies 2009; Bril 2010; Merkies 2010; Deng 2012
15	**Methotrexate** versus placebo	RMC 2009
16	**Interferon beta-1a** versus placebo	Hughes 2010
17	**Comparison of two different brands of IVIg**	Kuitwaard 2010
18	**Daily prednisolone** versus **monthly high dose dexamethasone** (PREDICT trial)	Van Schaik 2010*; Eftimov 2012
19	**IVIg** versus **intravenous methylprednisolone**	Nobile-Orazio 2015; Nobile-Orazio 2012*
20	**IVIg** versus **corticosteroids**	Camdessanché 2014
21	**Subcutaneous immunoglobulin** versus placebo	Harbo 2012; Markvardsen 2013*;Markvardsen 2012;
22	**Lipoic acid** versus placebo	NCT00962429
23	**Gullong tongluo capsule** versus no treatment	Hu 2009

Footnotes

Abbreviations: IVIg: intravenous immunoglobulin
*Primary reference where there is more than one reference. Trials are listed in order of publication of the primary reference.

4 Trials in progress

	Comparison	Reference
1	Subcutaneous human immunoglobulin versus placebo	Van Schaik 2016; NCT01545076
2	0.2 g/kg versus 0.4 g/kg subcutaneous human immunoglobulin	Markvardsen 2016
3	Fingolimod versus placebo	Hartung 2014; NCT01625182
4	Comparison of 2 different IVIg preparations	Pouget 2016
5	IVIg maintenance versus IVIg taper	Eftimov 2015
6	Dose-response trial of IVIg	Kuitwaard 2016

Footnotes

References to reviews

Included reviews

Eftimov 2013

Eftimov F, Winer JB, Vermeulen M, De Haan R, van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database of Systematic Reviews 2013;12:CD001797. [Art. No.: CD001797 DOI: 10.1002/14651858.CD001797.pub3; PubMed: 24379104]

Hughes 2015

Hughes RA, Mehndiratta MM. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database of Systematic Reviews 2015, Issue 1. Art. No.: CD002062 DOI: 10.1002/14651858.CD002062.pub3. [PubMed: 25561247]

Mahdi-Rogers 2013

Mahdi-Rogers M, van Doorn PA, Hughes RA. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD003280 DOI: 10.1002/14651858.CD003280.pub3. [PubMed: 21069674]

Mehndiratta 2015

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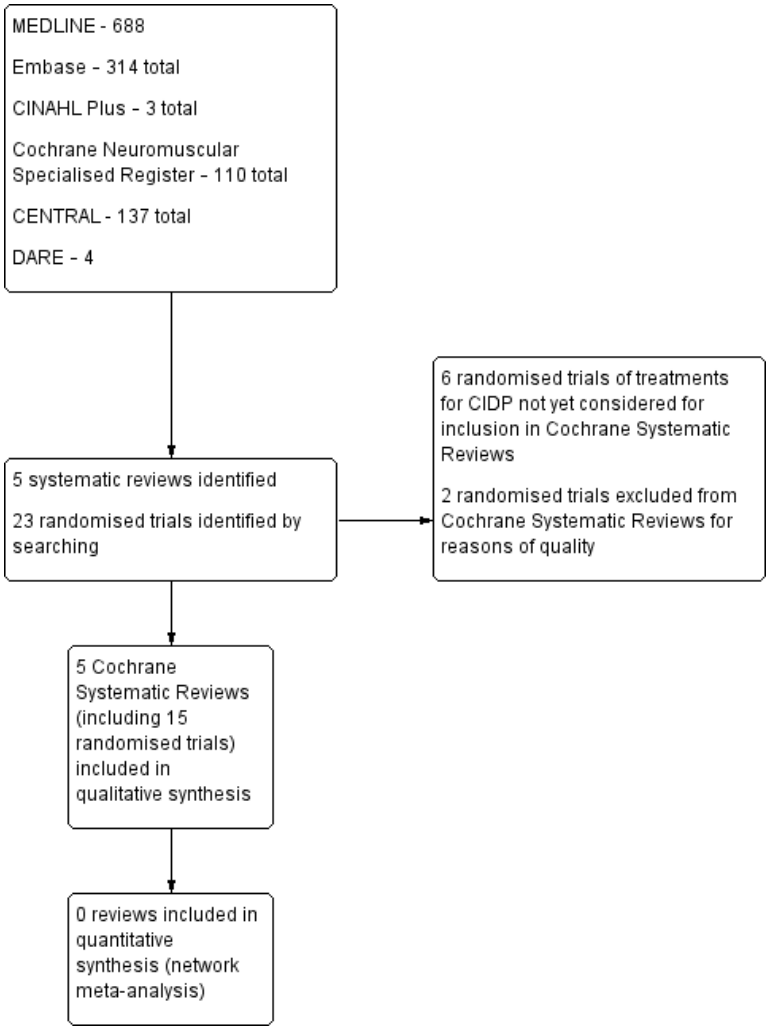
Figures

Figure 1



Caption

Study flow diagram. We are unable to calculate numbers of papers following deduplication and numbers reviewed in full text, as different authors reviewed several searches during development of the overview.

Sources of support

Internal sources

- National Institute for Health Research, Cochrane Review Group Infrastructure Award, UK
  Financial support

External sources

- GBS Support Group, UK
  Financial support

Feedback

Appendices

1 DARE search strategy

(This database is no longer being updated)

#1 inflammatory near/3 demyelinating
#2 polyradiculoneuropath* or polyneuropath* or polyneuritis or polyradiculoneuritis
#3 #1 and #2 and chronic
#4 MeSH descriptor: [Polyradiculoneuropathy, Chronic Inflammatory Demyelinating] this term only
#5 cidp
#6 #3 or #4 or #5

2 MEDLINE (OvidSP) search strategy

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Ovid MEDLINE(R) 1946 to October Week 3 2016

Search Strategy:
---
1 randomized controlled trial.pt. (434179)
2 controlled clinical trial.pt. (91862)
3 randomized.ab. (374639)
4 placebo.ab. (180548)
5 drug therapy.fs. (1920922)
6 randomly.ab. (266035)
7 trial.ab. (389797)
8 groups.ab. (1652938)
9 or/1-8 (3932161)
10 exp animals/ not humans.sh. (4333932)
11 9 not 10 (3392288)
12 Polyradiculoneuropathy, Chronic Inflammatory Demyelinating/ (1147)
13 ((chronic adj3 inflammatory adj3 demyelinating adj3 polyradiculoneuropathy) or (chronic adj3 inflammatory adj3 demyelinating adj3 polyneuropathy) or cidp).mp. (2341)
14 inflammatory demyelinating.tw. (4069)
15 (polyradiculoneuropath$3 or polyneuropath$3).tw. (13269)
16 (polyneuritis or polyradiculoneuritis).tw. (1979)
17 polyneuropathies/ or Polyradiculoneuropathy/ (8301)
18 or/15-17 (19443)
19 chronic disease.mp. (261544)
20 14 and 18 and 19 (329)
21 or/12-13,20 (2355)
22 11 and 21 (689)
23 meta-analysis/ (74900)
24 meta-analysis.pt. (74900)
25 (meta analy$ or metaanaly$ or meta?analy$).tw. (105559)
26 ((health technology adj5 assessment) or hta).tw. (4213)
27 (systematic adj3 review$).mp. (99105)
28 (systematic adj3 overview$).mp. (1148)
29 consensus development conference.pt. (10250)
30 practice guideline.pt. (22081)
31 or/23-30 (216633)
32 21 and 31 (53)
33 22 or 32 (710)
34 remove duplicates from 33 (688)

3 EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2016 Week 44>
Search Strategy:
---
1 crossover-procedure.sh. (53582)
2 double-blind procedure.sh. (136356)
3 single-blind procedure.sh. (26668)
4 randomized controlled trial.sh. (458122)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (1336628)
6 trial.ti. (212638)
7 or/1-6 (1492367)

8 (animal/ or nonhuman/ or animal experiment/) and human/ (1706635)
9 animal/ or nonanimal/ or animal experiment/ (3726774)
10 9 not 8 (3023844)
11 7 not 10 (1379659)
12 limit 11 to embase (487876)
13 (inflammatory adj3 demyelinating).tw. (6641)
14 (polyradiculoneuropath$3 or polyneuropath$3).tw. (18603)
15 polyneuropathies/ or Polyradiculoneuropathy/ (13564)
16 (polyneuritis or polyradiculoneuritis).tw. (1868)
17 or/14-16 (25476)
18 chronic disease.tw. or Chronic Disease/ (195443)
19 13 and 17 and 18 (130)
20 chronic inflammatory demyelinating polyneuropathy/ (2481)
21 (chronic adj3 inflammatory adj3 demyelinating adj3 polyradiculoneur$).tw. (1033)
22 cidp.mp. (2425)
23 or/19-22 (3977)
24 12 and 23 (111)
25 meta analysis/ (150972)
26 (meta analy$ or metaanaly$ or meta?analy$).mp. (191601)
27 biomedical technology assessment/ (11790)
28 ((health technology adj5 assessment) or hta).mp. (6410)
29 (systematic adj3 review$).mp. (181811)
30 or/25-29 (307392)
31 23 and 30 (79)
32 11 and 23 (284)
33 31 or 32 (334)
34 remove duplicates from 33 (314)

4 CINAHL Plus (EBSCOhost) search strategy

Monday, October 31, 2016 10:07:55 AM

S41 S32 OR S38 Limiters - Exclude MEDLINE records
Search modes - Boolean/Phrase 3
S40 S32 OR S38 Search modes - Boolean/Phrase 115
S39 Limiters - Exclude MEDLINE records
Search modes - Boolean/Phrase 2,266,641
S38 S31 AND S37 10
S37 S33 OR S34 OR S35 OR S36 87,988
S36 systematic N3 review* 67,411
S35 (MH "Systematic Review") 38,064
S34 meta analy* or metaanaly* or meta-analy* 41,856
S33 (MH "Meta Analysis") 25,408
S32 S18 and S31 115
S31 S28 or S29 or S30 417
S30 chronic n3 inflammatory n3 demyelinating n3 polyradiculoneuropathy 136
S29 cidp 236
S28 S22 and S26 and S27 370
S27 chronic 187,251
S26 S23 or S24 or S25 5,113
S25 polyradiculoneuropath* or polyneuropath* or polyneuritis 2,005
S24 (MH "Polyneuritis+") 331
S23 (MH "Polyradiculoneuritis+") or (MH "Polyradiculopathy") 3,493
S22 S21 or (S19 and S20) 676
S21 inflammatory n3 demyelinating 583
S20 TI inflammatory or AB inflammatory 44,115
S19 (MH "Demyelinating Diseases") 1,225
S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 862,610
S17 ABAB design* 92
S16 TI random* or AB random* 180,834
S15 (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial or sham? or dummy)) 358,285
S14 (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic)) and (TI (trial*) or AB (trial*)) 130,719
S13 (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or systematic review*)) 49,432
S12 (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind* or mask*)) 27,819

S11 PT ("clinical trial" or "systematic review") 131,814
S10 (MH "Factorial Design") 984
S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") 290,556
S8 (MH "Meta Analysis") 25,408
S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison") 50
S6 (MH "Quasi-Experimental Studies") 8,041
S5 (MH "Placebos") 9,846
S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies") 34,078
S3 (MH "Clinical Trials+") 203,602
S2 (MH "Crossover Design") 14,009
S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample") 73,894

5 Cochrane Neuromuscular Specialised Register (CRS) search strategy

#1 MeSH DESCRIPTOR Polyradiculoneuropathy, Chronic Inflammatory Demyelinating [REFERENCE] [STANDARD]
#2 (chronic NEAR3 inflammatory NEAR3 demyelinating NEAR3 polyradiculoneuropathy) or (chronic NEAR3 inflammatory NEAR3 demyelinating NEAR3 polyneuropathy) or cidp [REFERENCE] [STANDARD]
#3 "inflammatory demyelinating" [REFERENCE] [STANDARD]
#4 polyradiculoneuropathy or polyneuropathy or polyradiculoneuropathies or polyneuropathies [REFERENCE] [STANDARD]
#5 polyneuritis or polyradiculoneuritis [REFERENCE] [STANDARD]
#6 MeSH DESCRIPTOR Polyneuropathies [REFERENCE] [STANDARD]
#7 MeSH DESCRIPTOR Polyradiculoneuropathy [REFERENCE] [STANDARD]
#8 #4 or #5 or #6 or #7 [REFERENCE] [STANDARD]
#9 "chronic disease" [REFERENCE] [STANDARD]
#10 #3 and #8 and #9 [REFERENCE] [STANDARD]
#11 #1 or #2 or #10 [REFERENCE] [STANDARD]
#12 (#1 or #2 or #10) AND (INREGISTER) [REFERENCE] [STANDARD]

6 CENTRAL (CRSO) search strategy

#1 (inflammatory near3 demyelinating):TI,AB,KY
#2 (polyradiculoneuropath* or polyneuropath* or polyneuritis or polyradiculoneuritis):TI, AB, KY
#3 #1 and #2 and chronic
#4 MESH DESCRIPTOR Polyradiculoneuropathy, Chronic Inflammatory Demyelinating
#5 cidp:TI,AB,KY
#6 #3 OR #4 OR #5

7 Additional methods (as described in the protocol)

Where comparable data and outcomes existed for different treatments, we would have performed indirect comparisons between them using a network analysis and multiple treatments meta-analysis if appropriate (White 2011b). We would have judged formal multiple treatments meta-analysis to be appropriate if the reviews had included the same outcome in any meta-analyses and if the trial populations had been broadly comparable in age, gender, diagnostic criteria, disease duration and disease severity. We would have accepted limited variation in these parameters, provided that there had been some overlap. For example, if all participants in one meta-analysis had had 'mild' disease and those in another all 'moderate', then we would not have combined them formally. However, if the mixtures had been something like 30:70 in one meta-analysis and 70:30 in another, then we would have combined them but expressed the need for caution in interpretation. To be considered comparable the outcomes should have been measured in clinically equivalent ways in each meta-analysis over clinically similar periods of follow-up. In fact no indirect comparisons by network analysis were possible because of a lack of shared outcomes and outcome intervals with the different interventions.

The method of White 2011b places multiple-treatment meta-analysis within the wider context of multivariate meta-analysis. Our approach would have paralleled that described by White for his analysis combining data from 24 RCTs assessing four different smoking cessation interventions . We would have first fitted so-called 'consistency' models that assumed no design-by-treatment interactions and used these to estimate pairwise treatment differences (with 95% confidence intervals (CIs)) and between-studies heterogeneity. We would then have fitted 'inconsistency models' to assess the level of evidence for design-by-treatment interactions. If there had been evidence of such interactions then we would have sought to explain these using any relevant factors that differed between studies. As an example, consider three treatments A, B and C for which trials that directly compare A with B favour A, and trials that directly compare A with C favour C, but trials that compare B with C favour B. The data are contradictory unless one can identify a factor that explains the apparent discrepancy. For instance, if C is be the best treatment in “severe” cases, but the worst in “mild” cases, and the trials comparing A with C had been carried out predominantly in “severe” cases, but those comparing B with C had been carried out predominantly in “mild” cases, then this could explain the discrepancy. If there had been unexplainable design-by-treatment interactions, then our interpretation would have been suitably cautious.