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Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome.

Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD008630.

DOI: 10.1002/14651858.CD008630.pub4.

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Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

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Editorial group: Cochrane Neuromuscular Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 11, 2016.

Review content assessed as up-to-date: 18 January 2016.

Citation: Pritchard J, Hughes RAC, Hadden RDM, Brassington R. Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD008630. DOI: 10.1002/14651858.CD008630.pub4.

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ABSTRACT

Background

Plasma exchange and intravenous immunoglobulin, but not corticosteroids, are beneficial in Guillain-Barré syndrome (GBS). The efficacy of other pharmacological agents is unknown. This review was first published in 2011 and updated in 2013 and 2016.

Objectives

To assess the effects of pharmacological agents other than plasma exchange, intravenous immunoglobulin and corticosteroids for GBS.

Search methods

On 18 January 2016, we searched the Cochrane Neuromuscular Specialised Register, Cochrane Central Register of Controlled Trials, MEDLINE, and Embase for treatments for GBS. We also searched clinical trials registries.

Selection criteria

We included all randomised controlled trials (RCTs) or quasi-RCTs of acute GBS (within four weeks from onset) of all types and degrees of severity, and in individuals of all ages. We discarded trials that investigated only corticosteroids, intravenous immunoglobulin or plasma exchange. We included other pharmacological treatments or combinations of treatments compared with no treatment, placebo or another treatment. We also identified a number of non-randomised studies during the search, the results of which we considered in the Discussion.

Data collection and analysis

We followed standard Cochrane methodology.

Main results

We identified no new trials during this update of the review. In previous versions of this review we identified only very low quality evidence for four different interventions published in four studies. Each study had a high risk of bias in at least one respect. One RCT with 19 participants comparing interferon beta-1a and placebo showed no clinically important difference in any outcome between groups. Another with 10 participants comparing brain-derived neurotrophic factor and placebo showed no clinically important difference in any outcome between groups. A third with 37 participants comparing cerebrospinal fluid filtration and plasma exchange also showed no clinically important difference in any outcome between groups. In a fourth with 43 participants, the risk ratio for an improvement by one or more disability grade after eight weeks was greater with the Chinese herbal medicine tripterygium polyglycoside than with corticosteroids (risk ratio 1.47; 95% confidence interval 1.02 to 2.11); other outcomes in this trial showed no difference. Serious adverse events were uncommon with each of these treatments and in the control groups.

Authors' conclusions

The quality of the evidence was very low. Three small RCTs, comparing interferon beta-1a or brain-derived neurotrophic factor with placebo, and cerebrospinal fluid filtration with plasma exchange, showed no significant benefit or harm for any of the interventions. A fourth small trial showed that the Chinese herbal medicine, tripterygium polyglycoside, hastened recovery in people with GBS to a greater extent than corticosteroids, but this result needs confirmation. We were unable to draw any useful conclusions from the few observational studies we identified.

PLAIN LANGUAGE SUMMARY

Drug treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for acute Guillain Barré syndrome

Review question

We reviewed the evidence for drug treatment other than intravenous immunoglobulin, plasma exchange or corticosteroids for people with Guillain-Barré syndrome (GBS).

Background

GBS is an acute, paralysing disease caused by inflammation of the nerves. Symptoms are most severe within four weeks of onset. Between 3% and 13% of people with GBS die of its complications. A quarter need a ventilator to help with breathing. Recovery takes several weeks or months and is often incomplete. Plasma exchange (washing harmful substances out of the blood) and intravenous immunoglobulin (infusion of human antibodies harvested from blood donations) can help speed up the recovery of people with GBS. There is no evidence for the efficacy of corticosteroids. Despite these treatments, however, many people who develop GBS experience long-term disability. We need to find what other treatments have been tried as a basis for launching new trials.

Study characteristics

We found four trials in the first version of this review (conducted in 2011) and no fresh evidence upon updating in 2013 and 2016. The trials each tested a different treatment. The evidence provided was very low quality. One RCT with only 19 participants compared interferon beta-1a (a drug that is beneficial in multiple sclerosis) with placebo. Another with only 10 participants compared a nerve growth factor which, in theory, should be beneficial in people with GBS, with placebo. A third trial, with 37 participants, compared cerebrospinal fluid filtration (washing the nerve roots around the spinal cord) with plasma exchange. A fourth trial with 43 participants compared the Chinese herbal medicine tripterygium polyglycoside, which is thought to have anti-inflammatory properties, with corticosteroids. The first three trials received commercial company support. Support for the fourth trial is unknown.

Key results and quality of the evidence

None of these trials was large enough to confirm or refute the benefit or harm of any of these drugs in the treatment of people with acute GBS. The only trial which found a difference between treatments was the Chinese herbal medicine trial: participants receiving the herbal medicine were one and a half times more likely to have improved disability after eight weeks than those receiving corticosteroids. However, this estimate was uncertain and the authors did not report other clinical outcomes. Serious adverse events were uncommon with each of the four treatments investigated in the identified studies and rates did not differ significantly to those in the control groups. We identified very little evidence other than that from RCTs.

There is a need to develop and test new treatments for GBS, and to adopt more sensitive outcome measures. Two ongoing trials are testing a complement-inhibiting immunosuppressant drug called eculizumab.

The evidence is up to date to January 2016.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

IFNb-1a versus placebo for Guillain-Barré syndrome						
Patient or population: people with Guillain-Barré syndrome Settings: 4 UK hospitals (Bensa 2000) ¹ Intervention: IFNb-1a versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	IFNb-1a placebo versus				
Improvement in disability grade after 4 weeks	The mean improvement in disability grade after 4 weeks in the control group was 1.3 grades	The mean improvement in disability grade after 4 weeks in the intervention group was 0.1 grades lower (1.58 lower to 1.38 higher)		19 (1 study)	⊕○○○ very low ^{2,3}	Mean (SD) improvement in placebo group (n = 6) was 1.3 (1.5)
Improvement by one or more disability grade after 4 weeks	500 per 1000	540 per 1000 (210 to 1000)	RR 1.08 (0.42 to 2.77)	19 (1 study)	⊕○○○ very low ^{2,3}	
Death or disability after 12 months (not measured)	See comment	See comment	Not estimable	-	-	Not measured
Death	-	-	RR 1.5 (0.07 to 32.29)	19 (1 study)	⊕○○○ very low ⁴	1 of 13 died in the IFNb-1a group and 0 of 6 died in the control group

Participants with 1 or more serious adverse events	333 per 1000	306 per 1000 (77 to 1000)	RR 0.92 (0.23 to 3.72)	19 (1 study)	⊕○○○ very low ^{2,3}
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; IFNb-1a: interferon beta-1a; RR: risk ratio; SD: standard deviation

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Since there is only one trial, the assumed risk has been taken as that of the control group

² Potential for unblinding

³ Downgraded twice for serious imprecision

⁴ Downgraded three times for very serious imprecision

BACKGROUND

Description of the condition

Guillain-Barré syndrome (GBS) is an acute paralysing disease that causes the rapid development of weakness of the limbs and often the facial, swallowing and breathing muscles. Tingling and numbness usually occur in the limbs at the same time. The disease is usually due to multifocal inflammation of the spinal roots and peripheral nerves, especially their myelin sheaths. The axons are often damaged as a secondary consequence of the inflammatory response. In some cases the axons are the primary focus of the attack. The weakness can reach its nadir within a few days or within four weeks. In 25% of people affected the disease is sufficiently severe to require the use of artificial ventilation (Hughes 2005; Yuki 2012; van den Berg 2014). Between 3% and 13% of people with GBS die during the first year after onset (van den Berg 2013). Recovery takes several weeks or months and is often incomplete. The cause of GBS is still under investigation. The favoured hypothesis is that it is due to an autoimmune response directed against antigens in the peripheral nerves that is triggered by a preceding bacterial or viral infection. The triggering mechanism is incompletely understood but may be the consequence of molecular mimicry whereby antibodies or T cells stimulated by antigenic epitopes on the infecting microbe cross-react with neural epitopes. In the most common form of GBS in Europe and North America the underlying pathological process is acute inflammatory demyelinating polyradiculoneuropathy. The responsible antigen is likely to be in the Schwann cell membrane or the myelin sheath. Axonal forms of the disease are uncommon in Europe and North America but more common in China, Japan, India and Central America. In axonal varieties the axon membrane is probably the target of the immune response (Yuki 2012). Distinguishing the different forms of the disease during life is difficult but has been attempted through neurophysiological studies (Hadden 1998).

Description of the intervention

Evidence from randomised controlled trials (RCTs) summarised in Cochrane Reviews has shown that plasma exchange and intravenous immunoglobulin (IVIg), but not corticosteroids, have a beneficial effect in GBS by hastening recovery (Hughes 2007; Hughes 2012; Hughes 2012a; Raphael 2012). Plasma exchange and IVIg have reduced but not prevented prolonged stays in intensive care unit and hospital and long-term disability (Hughes 2012; Raphael 2012). Many people with GBS have persistent fatigue (Merkies 1999); 12% still require aid to walk one year after the onset of GBS (Rees 1998) and 62% still notice its effect on their own or their carers' lives three to six years later (Bernsen 1999). Exercise and rehabilitation programmes are used and evidence for their benefit is being sought (Bussman 2007; Demir 2008), but

it is likely that the need for improved pharmacological treatments will persist.

At the time of writing the protocol for this review (Hughes 2010c), we knew of two small placebo-controlled RCTs of interferon beta-1a (IFNβ-1a) (Pritchard 2003), an immunomodulating agent beneficial in multiple sclerosis, and brain-derived neurotrophic factor (Bensa 2000), a trophic factor known to be important in the development of motor neurons, in people with GBS. We also knew of a RCT comparing cerebrospinal fluid exchange with plasma exchange, undertaken on the ground that removal of harmful factors in the fluid surrounding the spinal roots would be beneficial (Wollinsky 2001). None of these trials showed statistically or clinically significant benefit of any of the interventions versus the comparators. It was possible that there were other published or unpublished RCTs of other agents which would be revealed by a systematic search. One new trial was indeed discovered. Zhang 2000 published a RCT of a Chinese herbal medicine in Chinese. In this trial the authors compared tripterygium polyglycoside, an extract of the Thunder God Vine, with corticosteroids and reported a significant beneficial effect. Tripterygium polyglycoside has anti-inflammatory properties and has been reported to be effective in inflammatory conditions such as rheumatoid arthritis (Goldbach-Mansky 2009).

Why it is important to do this review

The treating doctor has a responsibility to know about the evidence for all treatments which have been used for the condition under consideration, in this case GBS. It is also an ethical requirement to undertake a systematic review before embarking on trials of other agents to make sure that they have not already been tested. Such a review should help to identify appropriate agents, outcomes and trial designs. We therefore undertook this systematic review of RCTs of pharmacological treatments other than corticosteroids, IVIg and plasma exchange for GBS. The review was first published in 2011, previously updated in 2013 and now in 2016.

OBJECTIVES

To assess the effects of pharmacological agents other than plasma exchange, intravenous immunoglobulin and corticosteroids for GBS.

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs or quasi-randomised (using alternate or other systematic allocation) controlled trials. As anticipated, we also identified non-randomised studies of pharmacological treatments which had not been subjected to randomised trials. There is no method for searching systematically that would have identified all such studies. We noted in the [Discussion](#), case reports and case series discovered during the search for RCTs in which the diagnosis, treatment and results were sufficiently described to enable us to be confident of the diagnosis, and to deduce the pretreatment and outcome disability grade. Although not planned in the protocol we also searched our personal databases for non-randomised studies.

Types of participants

We included children and adults with GBS of all degrees of severity. GBS was defined according to internationally accepted diagnostic criteria (those of [Asbury 1990](#)) as acute polyradiculoneuropathy causing progressive weakness of two or more limbs, having an onset phase of not more than four weeks and reduced or absent tendon reflexes, and lacking alternative causes. We included acute inflammatory demyelinating polyradiculoneuropathy and axonal forms of the disease, although in practice the two forms were never distinguished in published reports of the included treatment trials. We included studies that did not conform exactly to these criteria provided that the authors regarded GBS or one of its synonyms, such as acute idiopathic neuropathy or acute inflammatory demyelinating polyradiculoneuropathy, as the preferred diagnosis. We noted any departure from the internationally accepted diagnostic criteria.

Types of interventions

We included all pharmacological treatments or combinations of treatments for acute GBS other than corticosteroids, IVIg and plasma exchange, compared with placebo, no treatment or another treatment. We confined our attention to treatments delivered in the acute stage to modify the duration and severity of clinical disease as defined by the outcome measures below. We defined acute as within the first four weeks after the onset of symptoms of weakness. We did not include treatments for symptoms of GBS unrelated to weakness or disability (for example, treatments for neuropathic pain or fatigue).

Types of outcome measures

Primary outcomes

We assessed the outcomes selected for previous Cochrane Reviews of treatments for GBS.

The primary outcome was improvement in disability grade ([Hughes 1978](#)) four weeks after randomisation. We tested the significance of the difference between each pharmacological treatment and placebo, no treatment or other treatments by calculating the mean difference (MD) and would have pooled the results in a meta-analysis if there had been more than one trial of a single intervention. This method of calculating the outcome is a more sensitive measure than change in proportions of participants improved.

We accepted the disability scale used by the authors of each trial provided that it was closely similar to that selected for this review ([Hughes 1978](#)) or could be adapted to correspond to that scale, now called the GBS disability scale:

1. healthy;
2. minor symptoms or signs of neuropathy but capable of manual work;
3. able to walk without support of a stick but incapable of manual work;
4. able to walk with a stick, appliance or support;
5. confined to bed or chair;
6. requiring assisted ventilation;
7. dead.

Secondary outcomes

1. Improvement by one or more GBS disability grade after four weeks.
2. Time from randomisation until recovery of unaided walking.
3. Time from randomisation until discontinuation of ventilation (for those ventilated).
4. Death.
5. Death or disability (inability to walk without aid) after 12 months.
6. Serious adverse events (that is adverse events which are life-threatening or fatal, or require or prolong hospital stay).

Search methods for identification of studies

On 18 January 2016, we searched the Cochrane Neuromuscular Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL in the Cochrane Register of Studies Online), MEDLINE (January 1966 to January 2016) and Embase (January 1980 to January 2016). We also searched ClinicalTrials.gov (www.clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/ictpr/en/), on 2 March 2015. We contacted trial authors and other experts in the field to identify additional published or unpublished data. We did not use a treatment term but discarded trials that investigated only corticosteroids, IVIg or plasma exchange during the selection process. We searched the references retrieved by the above process and our personal databases for non-

randomised cohort studies, case series and case reports in which the diagnosis, treatment and results were sufficiently described to deduce the pretreatment and outcome disability grade. We applied no language limitations.

Electronic searches

We provide the search strategies for the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, and the trials registries in [Appendix 1](#), [Appendix 2](#), [Appendix 3](#), [Appendix 4](#), and [Appendix 5](#), respectively.

Searching other resources

We contacted 13 trial authors or disease experts for information about other trials, including unpublished trials.

Data collection and analysis

Selection of studies

Two review authors checked titles and abstracts identified by the search and decided independently which should be studied further. We obtained the full text of all studies selected as being potentially relevant. Two review authors studied the full texts with the aid of a specially designed form and decided independently which fitted the inclusion criteria. We resolved disagreements about inclusion by discussion, if necessary with the help of the third review author. We have reported all the RCTs identified in the [Results](#) section. We have reported relevant non-randomised studies in the [Discussion](#).

Data extraction and management

Two review authors extracted data independently into specially designed forms. The review authors compared the forms and resolved disagreements by reference to the original reports. We attempted to obtain missing data from the trial authors. Additionally, for two studies that involved two review authors as trial authors, two other review authors, who had not been involved in the studies, independently extracted data using data extraction forms. For trials requiring translation, the translator extracted data into a data extraction form.

Assessment of risk of bias in included studies

Two review authors (RACH, RDMH or JP) independently assessed the risk of bias in each identified RCT using specially designed forms, using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). A third review author (RB) independently assessed risk of bias and data extraction for [Bensa 2000](#) and [Pritchard 2003](#) as these studies involved two review authors as trial authors. We considered the

following attributes: explicit diagnostic criteria, sequence generation, allocation concealment, blinding, completeness of follow-up, freedom from selective reporting and other sources of bias. We graded these items as at low, high or unclear risk of bias and described the evidence on which we based our conclusions in a 'Risk of bias' table. If the assessments differed, we obtained agreement by consensus, if necessary in consultation with a third author.

Measures of treatment effect

If meta-analysis of more than one trial of the same or comparable agents had been possible we would have calculated a weighted treatment effect across trials using the Cochrane statistical package, Review Manager (RevMan) 5 ([RevMan 5](#)). For dichotomous outcomes, such as 'improvement by one or more GBS disability grade after four weeks', we used RevMan to calculate a risk ratio (RR). For continuous outcomes we tested MDs. We expressed uncertainty with 95% confidence intervals (CIs). We used a fixed-effect approach for the analyses.

Dealing with missing data

We sought missing data from the trial authors and reported its absence when not available.

Assessment of heterogeneity

If there had been multiple trials of one intervention and evidence of significant heterogeneity between studies had been detected using the I^2 statistic, we would have sought explanations for the heterogeneity and, if none had been found, would have used a random-effects analysis.

Assessment of reporting biases

If there had been sufficient trials of one intervention we would have constructed funnel plots and inspected them for evidence of publication bias.

Data synthesis

If meta-analysis of more than one trial of the same or comparable agents had been possible we would have calculated a weighted treatment effect across trials using RevMan.

'Summary of findings' tables

We have provided a 'Summary of findings' table for each comparison and reported in them the primary and secondary outcomes for this review. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence (studies that contribute data for the prespecified outcomes), according to methods described in the *Cochrane Handbook for Systematic Reviews of*

Interventions (Schunemann 2011). We used GRADEpro software to prepare the tables (GRADEpro 2008). Using our assessments we drew conclusions about the quality of the evidence within the text of the review.

Subgroup analysis and investigation of heterogeneity

We would have liked to examine the effect of treatments in the following subgroups, chosen because of their prognostic importance in previous prospective studies and trials.

1. Younger and older participants (children aged less than 18 years; adults from age 18 to 49 years of age; adults aged 50 years or more).

2. Participants more severely or less severely affected (able to walk (GBS disability grades 1 to 3), unable to walk (grade 4), or requiring ventilation (grade 5) at randomisation).

3. Participants having or not having a documented relevant sensory deficit on routine neurological examination at randomisation (symptoms alone will be ignored).

4. Participants having or not having a history of diarrhoea (gastroenteritis) within the six weeks before the onset of neuropathic symptoms.

5. Time from onset of symptoms of neuropathy to start of treatment (seven days or less after onset, more than seven and up to 14 days after onset, and more than 14 days after onset).

6. Axonal versus demyelinating forms of GBS, defined by neurophysiological criteria (Hadden 1998).

No information was available for any of these subgroups.

Sensitivity analysis

If there had been more than one trial of one intervention we would have performed sensitivity analyses in which trials that had a high risk of bias were omitted from the meta-analysis.

RESULTS

Description of studies

Results of the search

The previous versions of this review included four completed RCTs. The search updates, in February 2015 and January 2016, identified the following new references: 37 in MEDLINE, 102 in Embase, 160 in CENTRAL and 75 in the Cochrane Neuromuscular Specialised Register. We identified no new trials for this update. See Figure 1 for a diagram illustrating the study selection process. We also identified two ongoing trials in ClinicalTrials.gov and the WHO Clinical Trials Registry Platform, each testing complement inhibition with eculizumab in addition to standard IVIg in severely affected people with GBS (Davidson 2014; JET-GBS 2015). Personal enquiry to 13 experts in the field yielded no more relevant studies.

Figure 1. Study flow diagram.

Included studies

We included two very small randomised, placebo-controlled, double-blind trials, one of IFN β -1a (Pritchard 2003) and one of brain-derived neurotrophic factor (BDNF) (Bensa 2000). We also included one small, randomised, open, controlled trial comparing CSF filtration with plasma exchange (Wollinsky 2001) and another comparing the Chinese herbal medicine tripterygium polyglycoside with intravenous corticosteroids (Zhang 2000).

Excluded studies

We have reported one historically controlled study of mycophenolate mofetil (Garssen 2007) and other non-randomised case series or case reports of other agents (Bos Eyssen 2011; Hammond 1993)

in the [Characteristics of excluded studies](#) and the [Discussion](#). We have only reported other excluded studies in [Characteristics of excluded studies](#). The most common reasons for exclusion were that the diagnosis was not clear or was not GBS, or that the intervention was not a pharmacological treatment.

Risk of bias in included studies

We have summarised the risk of bias for the included trials in [Figure 2](#) and [Characteristics of included studies](#). The very small trials of IFN β -1a and BDNF had a high risk of bias for blinding and baseline imbalance, respectively. The trial of CSF filtration had a high risk of bias for allocation concealment, blinding and individual analysis issues. The trial of tripterygium polyglycoside had a high risk of bias for blinding.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bensa 2000	+	+	+	+	+	-
Pritchard 2003	+	+	-	+	+	+
Wollinsky 2001	+	-	-	-	+	-
Zhang 2000	?	?	-	?	?	?

Effects of interventions

See: [Summary of findings for the main comparison](#) IFNb-1a versus placebo for Guillain-Barré syndrome; [Summary of findings 2](#) BDNF versus placebo for Guillain-Barré syndrome; [Summary of findings 3](#) CSF filtration versus plasma exchange for Guillain-Barré syndrome; [Summary of findings 4](#) Tripterygium polyglycoside versus corticosteroids for Guillain-Barré syndrome

Interferon beta-1a versus placebo

One small RCT with a low risk of bias other than that for blinding (see [Figure 2](#), [Characteristics of included studies](#) and [Summary](#)

[of findings for the main comparison](#)) randomised 13 participants with severe early GBS (unable to walk without aid and within two weeks from the onset of symptoms, mean disability grade 4.1) to IFNb-1a (Rebif) and six to placebo (mean disability grade 4.0) (Pritchard 2003). The drug or placebo was given by subcutaneous injection three times a week starting with 22 µg per injection for the first week and continuing with 44 µg for the subsequent 23 weeks. Participants stopped treatment if they became able to walk without aid (grade 2). The trial stopped after 24 weeks. The mean improvement in disability grade after four weeks was 1.2 grades (standard deviation (SD) 1.6) in the IFNb-1a group and 1.3 grades

(SD 1.5) in the placebo group. Thus, the difference in mean change in disability grade after four weeks was 0.10 (95% CI -1.38 to 1.58) of a grade less improvement in the IFNb-1a group ([Analysis 1.1](#)). Correspondingly, the RR of improvement by one or more GBS disability grade after four weeks was 1.08 (95% CI 0.42 to 2.77) in favour of IFNb-1a ([Analysis 1.2](#)). The median time (95% CI) to unaided walking was 59 (16 to infinity) days in the IFNb-1a group and 18 (11 to 70) days in the placebo group. The RR for death was 1.50 (0.07 to 32.29) greater in the IFNb-1a group ([Analysis 1.3](#)). The RR for having one or more serious adverse events was 0.92 (0.23 to 3.72), and thus was slightly lower in the IFNb-1a group ([Analysis 1.4](#)). None of the other differences reported by the authors was significantly different: these were outcomes after 24 weeks, and changes in Medical Research Council (MRC) sum score and grip strength at either four or 24 weeks. This study was much too small to exclude clinically important benefit or harm from IFNb-1a.

Brain-derived neurotrophic factor versus placebo

One very small RCT with a low risk of bias in all domains except that for other bias (see [Figure 2, Characteristics of included studies](#) and [Summary of findings 2](#)) randomised six participants with severe early GBS to BDNF (four disability grade 5 and 2 grade 4) and four to placebo (all grade 4) ([Bensa 2000](#)). The trial was terminated early because the manufacturer withdrew the drug after it was found to be ineffective in a trial for motor neuron disease. The drug, r-metHuBDNF 25 µg/kg, or placebo was given by daily subcutaneous injection for 24 weeks. Participants stopped treatment upon reaching GBS disability grade 2. None of the outcomes reported was significantly different between the groups. After four weeks there was 0.75 (95% CI -1.14 to 2.64) of a grade more improvement in the BDNF group than in the placebo group ([Analysis 2.1](#)). The RR for improvement by one or more GBS disability grade after four weeks was the same, 1.00 (95% CI 0.28 to 3.54), in both groups ([Analysis 2.2](#)). The time to unaided walking had a median (95% CI) value of 84 (4 to infinity) days in the BDNF group and 84 (2 to infinity) in the placebo group. The RR for death was 0.67 (95% CI 0.06 to 7.85), being lower in the BDNF group ([Analysis 2.3](#)). The RR for death or disability after 12 months was 1.33 (95% CI 0.17 to 10.25) more with BDNF than with placebo ([Analysis 2.4](#)). The RR for serious adverse events was 1.00 (0.28 to 3.54) ([Analysis 2.5](#)). There were no significant differences in the other outcomes reported, which were the arm disability grade assessed at the times given above, and the arm and overall disability grade at 12, 24 and 48 weeks. This study was much too small to exclude clinically important benefit or harm from BDNF.

Cerebrospinal fluid filtration versus plasma exchange

One RCT with a high risk of bias ([Figure 2, Characteristics of included studies](#) and [Summary of findings 3](#)) compared 17 par-

ticipants treated with CSF filtration with 20 who received a conventional course of five plasma exchanges, removing a total of 200 mL/kg to 250 mL/kg of plasma altogether ([Wollinsky 2001](#)). CSF filtration consisted of removing, filtering and re-infusing 30 mL to 50 mL CSF five to six times a day for between 5 and 15 consecutive days. Of the 17 participants treated with CSF filtration four had disability grade 5 and 13 disability grade 4 at randomisation. Of the 20 who received plasma exchanges two had disability grade 5 and 18 disability grade 4 at randomisation. The outcomes selected for this review showed no significant differences between the groups. The mean improvement in disability grade after four weeks was almost exactly the same in both groups: MD 0.02 (95% CI -0.62 to 0.66) more in the CSF filtration group than in the plasma exchange group ([Analysis 3.1](#)). Similarly, the number of participants with one or more grade of improvement in both groups was similar: RR 0.94 (95% CI 0.48 to 1.84) in favour of the plasma exchange group ([Analysis 3.2](#)). These CIs were consistent with a halving or almost doubling of the number. The time until recovery of unaided walking in the surviving participants was shown by the authors in a Kaplan-Meier figure of an analysis from which nine participants were censored. From this published figure, we estimated the median (range) time until recovery of unaided walking as 42 (13 to 433) days in the CSF filtration group and 90 (6 to 420) days in the plasma exchange group. The authors commented that the times were similar in both groups. There was one death in each group: RR 1.18 (95% CI 0.08 to 17.42) in favour of the plasma exchange group ([Analysis 3.3](#)). Four participants in the plasma exchange group had serious adverse events compared with none in the CSF filtration group: RR 0.13 (95% CI 0.01 to 2.25) in favour of CSF filtration ([Analysis 3.4](#)). One participant in each group had side effects leading to cessation of treatment: RR 1.18 (95% CI 0.08 to 17.42) ([Analysis 3.5](#)). The small sample sizes in this trial prevent drawing conclusions about the relative efficacy of CSF filtration and plasma exchange. As explained in the [Discussion](#), this treatment is no longer being used because of the danger of producing an inflammatory reaction in the CSF.

Tripterygium polyglycoside versus intravenous high-dose corticosteroids

One RCT with an unclear risk of bias except for blinding, which was at high risk ([Figure 2, Characteristics of included studies](#) and [Summary of findings 4](#)), compared 22 participants treated with the Chinese herbal medicine tripterygium polyglycoside (randomisation disability grade 2 in six, 3 in 12 and 4 in three) with 21 participants treated with high-dose corticosteroids (randomisation disability grade 2 in 7, 3 in 11 and 4 in three) ([Zhang 2000](#)). The trial did not report the primary outcome for this review but after eight weeks, 20 of 22 participants treated with tripterygium polyglycoside had improved by one or more disability grade compared with 13 of 21 treated with high-dose corticosteroids: RR 1.47 (95% CI 1.02 to 2.11; [Analysis 4.1](#)). Only one adverse event was reported:

gastrointestinal toxicity in one person treated with tripterygium polyglycoside ([Analysis 4.2](#)). Other clinical outcomes and the outcomes for this review were not reported.

ADDITIONAL SUMMARY OF FINDINGS [\[Explanation\]](#)

BDNF versus placebo for Guillain-Barré syndrome						
Patient or population: people with Guillain-Barré syndrome Settings: 1 Canadian and 2 UK hospitals (Pritchard 2003) ¹ Intervention: BDNF versus placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	BDNF versus placebo				
Improvement in disability grade after 4 weeks	The mean improvement in disability grade after 4 weeks in the control group was 0.25	The mean improvement in disability grade after 4 weeks in the intervention group was 0.75 higher (1.14 lower to 2.64 higher)		10 (1 study)	⊕○○○ very low ²	Mean (SD) improvement in placebo group (n = 4) was 0.25 (1.71)
Improvement by one or more disability grade after 4 weeks	500 per 1000	500 per 1000 (140 to 1000)	RR 1.00 (0.28 to 3.54)	10 (1 study)	⊕○○○ very low ²	
Death or disability after 12 months	250 per 1000	332 per 1000 (43 to 1000)	RR 1.33 (0.17 to 10.25)	10 (1 study)	⊕○○○ very low ²	
Death	250 per 1000	168 per 1000 (15 to 1000)	RR 0.67 (0.06 to 7.85)	10 (1 study)	⊕○○○ very low ²	

Participants with 1 or more serious adverse events	500 per 1000	500 per 1000 (140 to 1000)	RR 1.00 (0.28 to 3.54)	10 (1 study)	⊕○○○ very low ²
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>BNDF: brain-derived neurotrophic factor; CI: confidence interval; RR: risk ratio; SD: standard deviation</p>					
<p>GRADE Working Group grades of evidence</p> <p>High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>Very low quality: We are very uncertain about the estimate.</p>					

¹ Control group has been used to provide assumed risk

² Downgraded three times for very serious imprecision

CSF filtration versus plasma exchange for Guillain-Barré syndrome						
Patient or population: people with Guillain-Barré syndrome Settings: one German hospital (Wollinsky 2001) ¹ Intervention: CSF filtration versus plasma exchange						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	CSF filtration versus plasma exchange				
Improvement in disability grade after 4 weeks	The mean improvement in disability grade after 4 weeks in the control group was 0.8	The mean improvement in disability grade after 4 weeks in the intervention group was 0.02 higher (0.62 lower to 0.66 higher)		31 (1 study)	⊕○○○ very low ^{2,3}	Mean (SD) improvement in plasma exchange group was 0.8 (0.95)
Improvement by one or more disability grade after 4 weeks	500 per 1000	470 per 1000 (240 to 920)	RR 0.94 (0.48 to 1.84)	37 (1 study)	⊕○○○ very low ^{2,3}	
Death or disability after 12 months	See comment	See comment	Not estimable	-	-	Not measured
Death	50 per 1000	59 per 1000 (4 to 871)	RR 1.18 (0.08 to 17.42)	37 (1 study)	⊕⊕○○ low ³	
Participants with 1 or more serious adverse events	200 per 1000	26 per 1000 (2 to 450)	RR 0.13 (0.01 to 2.25)	37 (1 study)	⊕○○○ very low ^{2,3}	

Adverse events leading to cessation of treatment	50 per 1000	59 per 1000 (4 to 871)	RR 1.18 (0.08 to 17.42)	37 (1 study)	⊕○○○ very low ^{2,3}
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio</p>					
<p>GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.</p>					

¹ The assumed risk has been taken as the risk on the plasma exchange group.

² Not blinded.

³ Downgraded twice for serious imprecision

Tripterygium polyglycoside versus corticosteroids for Guillain-Barré syndrome						
Patient or population: people with Guillain-Barré syndrome Settings: China (Zhang 2000) ¹ Intervention: Tripterygium polyglycoside versus corticosteroids						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Corticosteroids	Tripterygium polyglycoside				
Improvement in disability grade after 4 weeks (not reported)	See comment	See comment	Not estimable	-	-	Not reported
Improvement by one or more disability grade after 4 weeks	619 per 1000	910 per 1000 (631 to 1000)	RR 1.47 (1.02 to 2.11)	43 (1 study)	⊕○○○ very low ^{2,3,4}	This outcome was not one selected for this review
Death or disability after 12 months	See comment	See comment	Not estimable	-	-	Not measured
Death	See comment	See comment	Not estimable	43 (1 study)		No deaths reported in this study in either the tripterygium or corticosteroid groups
Participants with 1 or more serious adverse events	See comment	See comment	Not estimable	-	-	Not reported
Adverse events	0 per 1000	0 per 1000 (0 to 0)	RR 2.87 (0.12 to 66.75)	43 (1 study)	⊕○○○ very low ^{2,3,4}	1/21 with tripterygium 0/21 with corticosteroids

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Assumed risk has been taken as that of the corticosteroid group.

² Chinese text. Risk of bias classified as unclear by translator. Oral tripterygium versus intravenous corticosteroids: unblinded (downgraded for study limitations)

³ Primary outcome for this review was to be measured at 4 weeks but the only available data come from 8 weeks (downgraded for indirectness)

⁴ Downgraded for serious imprecision

DISCUSSION

Summary of main results

Overall summary

Many people have long-term disability after GBS despite treatment with IVIg or plasma exchange. There is therefore a need for better treatments. Unfortunately very few other treatments have been tested and those only in very small studies. This review identified four small RCTs, each providing only very low quality evidence. Trial participants who received the Chinese herbal medicine tripterygium polyglycoside had a better outcome after eight weeks compared with those receiving high-dose corticosteroids. None of the other three trials (of BDNF, IFNb-1a and CSF filtration) was large enough to identify or exclude clinically significant benefit or harm for any of the interventions: the CIs in these trials were so wide that the results were consistent with at least half a grade more or less improvement after 4 weeks. A half grade has been considered to be an amount which is clinically important (Plasma 1997).

Consideration of treatments tested in controlled trials

Small trials of three treatments did not show clinically important benefit but it may be premature to abandon interest in two of the three treatments.

1. For **BDNF**, there is now experimental evidence for a neuroprotective role of BDNF in mouse experimental allergic encephalomyelitis (Linker 2010). There are no other case reports or series investigating the use of BDNF in GBS. The use of neurotrophic factors to protect nerves from axonal degeneration and to encourage regeneration remains a possible strategy for the future. Research is needed into the optimal combination, route and dose of trophic factors.

2. For **IFNb-1a**, there are theoretical reasons to expect a beneficial effect in GBS. In multiple sclerosis, there is strong evidence that IFNb-1a is effective in reducing inflammation in the brain and the frequency of relapses (Rice 2001). In chronic inflammatory demyelinating polyradiculoneuropathy, neither of two small trials showed IFNb-1 to have a significant effect, but a post hoc analysis in one raised the possibility of an IVIg-sparing effect in participants who received large doses of IVIg (Hughes 2010b; Mahdi-Rogers 2010). In GBS, in addition to the small trial identified in this review (Pritchard 2003), there are two case reports of improvement following the use of IFNb-1a (combined with other treatments) (Créange 1998; Schaller 2001), but this could merely reflect the natural history of the disease. The trial included in this review did not identify significant safety concerns and, although the trend of the results was worse in the

IFNb-1a group than in the placebo group, the CIs were very wide (Pritchard 2003). Further trials of IFNb-1a could be considered.

3. The trial of **CSF filtration** was too small to prove that this intervention is equivalent in efficacy to plasma exchange in people with GBS. Before this trial was performed a series of 24 people with acute GBS had been treated with CSF filtration: their median time to improve one GBS disability grade was 19 days and their median time to walk unaided was 42 days (Wollinsky 1995). Insufficient information was published for us to judge the clinical significance of these findings and, in the absence of contemporary controls, we are not able to draw conclusions from this series. There have been no subsequent published case reports or series of the use of CSF filtration in GBS. Although there were no serious adverse events in the trial, CSF lymphocytic pleocytosis was noted in 14 of 14 people in whom this was assessed (Wollinsky 2001). There is a theoretical risk that CSF filtration may cause meningitis. Meningitis was observed in one participant in the trial but was attributed to an earlier lumbar puncture. However, granulocytic reactions have been observed in up to 20% of people with GBS and the procedure has been discontinued in the department responsible for this trial (Ludolph 2010 [pers comm]). The theoretical basis for this treatment was that inflammation of the spinal roots is an important part of the pathogenesis of GBS and that CSF filtration would remove “blocking factors” which block nerve conduction (Brinkmeier 1992). However, the inflammation in GBS also affects the nerve trunks and terminals (Feasby 2001), and the existence of “blocking factors” has been questioned (Cummins 2003; Otto 2005).

One small trial did show a clinically important benefit in people with GBS. This trial compared tripterygium polyglycoside with high-dose intravenous corticosteroids (Zhang 2000). The trial was small, had a high risk of bias and the outcome ‘improvement by one or more GBS disability grade after eight weeks’, in favour of tripterygium polyglycoside, was only barely statistically significant. The outcome after four weeks stipulated for this review was not available so this conclusion must be viewed with caution. This finding, if real, could have been due to a beneficial effect of tripterygium polyglycoside or a deleterious effect of corticosteroids. A Cochrane Review assessing the efficacy of corticosteroids for the treatment of people with GBS concluded that corticosteroids given alone do not have a significant beneficial or harmful effect (Hughes 2012a), so a beneficial effect of tripterygium polyglycoside is more likely. Zhang 2000 reported that tripterygium polyglycoside lowered inflammatory cytokine interleukin-6 concentrations in the serum to a significantly greater extent than corticosteroids. There are no other reports of the use of tripterygium polyglycoside in GBS. Tripterygium glycoside is an extract from the herb *Tripterygium wilfordii* which has been used as an anti-inflammatory agent in traditional Chinese medicine for many years. There are reports of benefits with this agent in RCTs investigating the prevention of renal allograft rejection and the treatment of Crohn's disease and

rheumatoid arthritis (Goldbach-Mansky 2009). Further study of the efficacy and side effects of tripterygium polyglycoside in GBS would be appropriate. However, such further investigation will be difficult because there are 380 metabolites in the ingredients of tripterygium extracts and no standardised method of extraction. The most active ingredients are terpenoids, some of which have been shown to inhibit key pathways in T cell activation and cyclooxygenase and nitric oxide production (Goldbach-Mansky 2009).

Mycophenolate mofetil

Mycophenolate mofetil has been licensed since 1996 for use “in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants” (Roche). It is often used in autoimmune diseases but the evidence for its efficacy is limited. In one review, mycophenolate mofetil was as effective as, but safer than, cyclophosphamide in the treatment of individuals with proliferative lupus nephritis (Mak 2009). In another, there was limited evidence of greater efficacy than azathioprine in people with pemphigus vulgaris (Martin 2009). In other diseases, such as myasthenia gravis, the RCTs performed have provided no evidence of efficacy (Sanders 2008; Burns 2015), but the absence of evidence may reflect lack of power in these studies and not necessarily a lack of efficacy.

Mycophenolate mofetil has been investigated in one non-randomised (therefore having a high risk of bias), historically controlled clinical trial in GBS, which compared 26 participants treated with oral mycophenolate mofetil 1000 mg a day for six weeks with 112 participants who had been treated without the drug in a previous RCT run by the same investigators in the same centres (van Koningsveld 2004; Garssen 2007). The participants treated with mycophenolate mofetil and the historical controls were simultaneously treated with IVIg 0.4 g IVIg/kg/day and intravenous methylprednisolone 500 mg/day for five consecutive days. There were no significant differences reported between the groups for any of the outcomes measured. The mean change in disability grade was not given. The RR of improving one disability grade after four weeks was 0.91 (95% CI 0.65 to 1.26) less in the mycophenolate mofetil group than in the controls, but included the possibility of a better or worse outcome in the mycophenolate mofetil group. The median time to improve to unaided walking was 70 days in the mycophenolate mofetil group and 28 days in the historical controls, a difference which was not significant when survival curves were compared using Kaplan-Meier methodology ($P = 0.22$). The RR for death was 1.44 (95% CI 0.31 to 6.71) greater in the historical control group but included the possibility of a greater or lesser RR than in the mycophenolate mofetil group. One of the mycophenolate mofetil participants had to discontinue the study drug temporarily because of abdominal complaints. The follow-up was limited to six months so that 12-month outcomes were not reported. There were no significant differences reported in other outcomes measured, which included the ability to walk

independently after eight weeks, time to improve one disability grade, need for artificial ventilation, MRC sum score and sensory impairment. There was no trend towards greater improvement with mycophenolate mofetil 1000 mg/day in this historically controlled study.

There are no other case reports or series on the use of mycophenolate mofetil in GBS. Since the dose used in the GBS trial was only 1000 mg daily, half the dose usually recommended in other autoimmune conditions, a higher dose should be considered if it were decided to pursue this drug in GBS.

Selective digestive tract decontamination

Selective digestive tract decontamination (SDD) has been tested in a retrospective study of 124 mechanically ventilated people with GBS comparing people in centres in which SDD was standard treatment with those in other centres where it was not (Bos Eyssen 2011, Table 1). The results suggested that SDD reduced the time on the ventilator, probably by preventing pneumonia. It did not affect neurological recovery after six months. Because of the lack of randomisation and the possibility of unrecognised confounding factors, this result requires confirmation. However, this treatment has been extensively tested in 36 trials involving 6914 people admitted to intensive care units. The participants had a wide variety of conditions and were not necessarily on artificial ventilation. According to the relevant Cochrane Review (D’Amico 2009), a combination of topical and systemic antibiotics significantly reduced respiratory tract infections and mortality whilst topical antibiotics alone significantly reduced respiratory tract infections but not mortality. Our search, conducted for this review on GBS, identified one trial of SDD which included 15 participants with GBS out of its whole sample of 40 participants with various neurological diseases (Hammond 1993). This trial on its own did not show significant reductions in the incidence of infections, the duration of intensive care unit or hospital stay, or mortality. The detailed results of this trial are given in the [Characteristics of excluded studies](#). Separate results for the participants with GBS are not available.

Other treatments studied in case reports and case series

Only three other treatments, azathioprine, cyclophosphamide and the anti-T-cell antibody muromonab-CD3 (OKT3), have been reported in observational studies fulfilling the criteria for inclusion in this [Discussion](#) (Table 1). Yuill 1970 reported the use of azathioprine in one person with severe GBS who was left with only mild deficit after five months. Cyclophosphamide was used in two small series of people with GBS. Ahuja 1980 treated four people with severe GBS with 100 mg cyclophosphamide daily (route not stated) starting between 3 and 28 days after onset. All improved and there were no serious adverse events, but one person had to

stop treatment because of diarrhoea. [Rosen 1976](#) reported a series of 15 people with GBS treated with cyclophosphamide 40 mg/kg intravenously, 12 of whom had severe GBS. Ten of the 12 improved by four weeks. Three eventually died. Reversible alopecia was common. The muromonab-CD3 monoclonal antibody against T cells was used in three people with severe GBS ([Feasby 1991](#)) but the results were not encouraging ([Table 1](#)). None of these studies was large enough to confirm or refute the clinically significant benefit or harm of any of these interventions.

Immunosuppression causing GBS

There are many reports of GBS occurring in people who are immunodeficient because of disease (such as Hodgkin's disease or HIV), iatrogenic immunosuppression for peripheral blood stem cell transplants (26 cases after allografts and 7 after autografts) ([Ostronoff 2008](#)), solid organ transplant ([Zhang 2008](#)) or autoimmune disease ([Hughes 1990](#)). Recent examples include GBS or GBS-like illnesses following interference with different components of the immune pathway. These include the antibody rituximab directed against the B-cell antigen CD20 (three people) ([Jaso 2010](#)), the tumour necrosis factor antagonists infliximab (11 people), etanercept (five) and adalimumab (seven) ([Alvarez-Lario 2013](#)), bortezomib for myeloma ([Ravaglia 2008](#)), pegylated interferon alpha-2a for hepatitis C infection ([Khiani 2008](#)) and the antibody efalizumab against the anti-CD11a component of lymphocyte function antigen 1 (four people: this drug has now been withdrawn from the market because of the occurrence of cases of progressive multifocal leukoencephalopathy) ([Victor 2008](#); [Turatti 2010](#)). These reports might merely be a testament to the enthusiasm of doctors to report unusual occurrences and be coincidences. If the association is real, it is a timely reminder of our limited understanding of the pathogenesis of GBS. This review has not attempted an exhaustive review of this literature.

Need for more trials

Further studies of tripterygium polyglycoside are needed, to identify its active ingredients, and confirm its efficacy and adverse effects. The complement-inhibiting drug eculizumab is the only agent at present on trial ([Davidson 2014](#); [JET-GBS 2015](#)). With the availability of many other agents that have been shown to be efficacious in inflammatory diseases, such as rheumatoid arthritis and multiple sclerosis, it is remarkable that so little work has been or is being done to test new immunosuppressive regimens in GBS. This systematic review establishes this lack of evidence and provides the basis on which future trials of these regimens can be launched. Future trials will need to use a standard GBS disability grade scale to facilitate comparison with previous trials. However, new, more responsive scales, with validated, preferably linear, biometric properties would be advantageous and should be developed. The new Rasch-built Overall Disability Scale (RODS) has been developed for this purpose and will be accepted in future

updates of this review ([Draak 2014](#)). Future trial design should take into account the minimum clinically important difference of the selected outcome measure ([Merkies 2010](#)).

Overall completeness and applicability of evidence

The evidence from published RCTs is likely to be complete because we have made use of the methods of the Cochrane Collaboration to search the literature. The evidence from the case studies and series cannot be complete since there is no known search strategy that will detect all published non-randomised studies. We did not discover any unpublished studies and the search for such studies is even less likely to be complete than that for published studies.

Quality of the evidence

The strength of the evidence from the RCTs is limited by the very small number of participants randomised in all studies and the lack of clarity about the risk of bias in the trial of tripterygium polyglycoside. The evidence from the study of mycophenolate mofetil is limited by the lack of randomisation.

Potential biases in the review process

This review might be biased by the fact that RACH co-authored two of the four included RCTs; one with JP and one with RDMH. We took steps to address this: two review authors who were independent of the trials also extracted and checked data, and independently assessed risk of bias. Two of the authors (RACH, RDMH) have received funding from companies that manufacture medications which are used or might be used for treating GBS (see [Declarations of interest](#)). All four RCTs were too small to detect rare serious adverse events.

Agreements and disagreements with other studies or reviews

We know of no other systematic reviews of pharmacological treatments other than corticosteroids, IVIg or plasma exchange for GBS.

AUTHORS' CONCLUSIONS

Implications for practice

The quality of the evidence from randomised controlled trials (RCTs) was very low. Three RCTs of pharmacological agents

other than intravenous immunoglobulin, plasma exchange or corticosteroids did not show a clinically important effect in people with GBS, one testing interferon beta-1a against placebo, another brain-derived neurotrophic factor against placebo, a third cerebrospinal fluid filtration against plasma exchange. None were large enough to show or refute clinically important benefit or harm. A fourth trial suggested that the Chinese herbal medicine tripterygium polyglycoside was superior to corticosteroids in hastening the recovery of people with GBS but the result requires confirmation. According to very low-quality evidence from one historically controlled trial, a low dose of the immunosuppressive drug mycophenolate mofetil shows no benefit in GBS. There have been very few observational studies and no randomised trials of other agents.

Implications for research

Since currently used immunotherapy does not prevent prolonged illness and leaves many people with GBS with clinically important residual disability, there is a need to discover and test new treatments for Guillain-Barré syndrome (GBS). Further investigation of the active ingredients of tripterygium polyglycoside and its mechanism, speed of action, and benefits and harms in GBS

would be appropriate.

ACKNOWLEDGEMENTS

We thank Jingjing Zhang, West China Hospital of Sichuan University, for translating and extracting data from five Chinese papers, one of which was an included study in this review (Zhang 2000). The translator is not related to the author of Zhang 2000. We thank Dong-Xing Wang, The Second Affiliated Hospital of Soochow University, for an additional translation.

The Cochrane Neuromuscular Disease Group Trials Search Coordinator, Angela Gunn, developed the search strategies with the review authors and ran the searches.

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

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- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bensa 2000

Methods	Double-blind, parallel-group, RCT
Participants	10 participants aged between 18 and 75 years with GBS fulfilling Asbury 1990 criteria within 14 days from the onset of symptoms and having Hughes 1978 disability grade > 3
Interventions	Daily subcutaneous injections of r-metHuBDNF 25 µg/kg (n = 6) or placebo (n = 4) (vehicle for active treatment, i.e. 150 mM sodium chloride with 0.004% polysorbate 20 buffered to pH 7 with 10 mM sodium phosphate) in vials identical in appearance for 24 weeks or until unaided walking achieved, if earlier
Outcomes	Primary: to investigate safety of r-metHuBDNF Secondary: to conduct a pilot investigation of the effects of treatment on overall disability after 24 and 48 weeks
Funding source	Amgen funded the trial and provided the drug and placebo
Declarations of interest	Not given in the paper but the investigators had no relationship with Amgen other than funding of the trial
Notes	Investigators intended to randomise 14 participants to r-metHuBDNF and 7 to placebo but the trial was curtailed prematurely because the manufacturer removed the drug from the market after negative results in a trial of its use in motor neurone disease Dates: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomised by opening an opaque sealed envelope that contained the code number of treatment to be received"
Allocation concealment (selection bias)	Low risk	"The pharmacist dispensed the coded medication that consisted of r-metHuBDNF 25 µg/kg or placebo in vials identical in appearance. Only the trial statistician and the pharmaceutical company knew the identity of the contents"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The patients were randomised by opening an opaque sealed envelope that contained the code number of treatment to be received. The pharmacist dispensed the coded medication that consisted of r-metHuBDNF 25 µg/kg or placebo in

Bensa 2000 (Continued)

		vials identical in appearance. Only the trial statistician and the pharmaceutical company knew the identity of the contents"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete case analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	BDNF participants had more severe disease and were randomised later. The numbers were insufficient to identify even a large effect

Pritchard 2003

Methods	Double-blind, randomised, parallel-group trial with 2:1 IFNb-1a to placebo ratio
Participants	19 people with GBS fulfilling Asbury 1990 criteria within 14 days from the onset of symptoms and having Hughes 1978 disability grade > 2
Interventions	IFNb-1a (Rebif) by subcutaneous injection 3 times a week starting with 22 µg per injection for the first week and continuing with 44 µg for subsequent weeks until a total of 24 weeks (n = 13) or placebo (n = 6). Participants stopped treatment upon reaching grade 2
Outcomes	Improvement in disability grade 4 weeks after randomisation, improvement by 1 or more disability grades 4 weeks after randomisation, time from randomisation to recovery of unaided walking Serious adverse events (defined as "fatal, life threatening, requiring or prolonging hospitalization, severely or permanently disabling, a new malignancy, or a known or suspected overdose")
Funding source	Serono International provided financial support and supplied the drug and placebo
Declarations of interest	The trial authors declared receipt of honoraria or travel grants and departmental research grants from Serono International
Notes	Participants in both groups received IVIg. This was a safety and tolerability study. There was no unexpected interaction with IVIg. A significant effect on efficacy outcomes was not expected because of the small sample size

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each centre was given study drug in a computer-generated (information from the authors) random sequence by the trial statis-

Pritchard 2003 (Continued)

		tician balanced to achieve a 2:1 ratio of IFNb-1a to placebo
Allocation concealment (selection bias)	Low risk	Each centre was given study drug in random sequence balanced to achieve a 2:1 ratio of IFNb-1a to placebo and concealed until all outcome measures, including attribution of causality of adverse events, had been collected
Blinding (performance bias and detection bias) All outcomes	High risk	No attempt was made to mask skin lesions from assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete case analysis reported
Selective reporting (reporting bias)	Low risk	Complete case analysis of all outcomes reported
Other bias	Low risk	None detected

Wollinsky 2001

Methods	Parallel-group, open, randomised trial	
Participants	37 people with GBS fulfilling standard Asbury criteria, unable to walk 5 m unaided, < 30 days from onset, age > 15 years	
Interventions	CSF filtration 30 to 50 mL removed, filtered and reinfused usually 5 to 6 times daily for 5 to 15 consecutive days (n = 17) versus plasma exchange total 200 to 250 mL/kg in 5 or 6 treatments daily or on alternate days for 7 to 14 days (n = 20)	
Outcomes	GBS disability grade after 28 and 56 days, side effects and lack of improvement after 56 days	
Funding source	Pall Medical (Dreieich, Germany) supplied filters and bidirectional pumps, and authors acknowledged financial support from L and B Brandt	
Declarations of interest	Not stated	
Notes	-	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Wollinsky 2001 (Continued)

Random sequence generation (selection bias)	Low risk	“by means of Documenta Geigy table”
Allocation concealment (selection bias)	High risk	“Blocks of two. Investigators aware of block size”
Blinding (performance bias and detection bias) All outcomes	High risk	All outcomes except death. No mention of blinding assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	The scores of 2 participants, one from each group, who died were carried forward with the last score before death and the score was not given
Selective reporting (reporting bias)	Low risk	Complete case analysis of all outcomes reported
Other bias	High risk	Two participants who underwent plasma exchange had transverse myelitis and were retained in the analysis without presentation of the results without them One participant in each group was crossed over: it was not possible to place a catheter in the CSF filtration participant. The plasma exchange participant went into hypovolaemic shock. In both cases the last value on the initial treatment was carried forward but the actual value was not given

Zhang 2000

Methods	Parallel-group, RCT
Participants	43 people with GBS diagnosed according to Asbury 1990 criteria
Interventions	Oral tripterygium polyglycoside (a Chinese herbal medicine) 60 to 80 mg daily for 4 weeks and then 30 to 45 mg daily for 4 further weeks (n = 22), versus intravenous dexamethasone 15 to 20 mg daily for 15 days, then 5 to 10 mg daily for 7 days, then oral prednisone 30 to 60 mg daily decreased by 5 to 10 mg daily every 2 weeks (n = 21)
Outcomes	Number improved at 8 weeks, adverse events and serum interleukin-6 concentrations
Funding source	Unknown
Declarations of interest	Information not given in the translation
Notes	English abstract available. Data extracted from full text by translator

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Divided into two groups on layer randomize principle" but method not described according to the translator
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Oral tripterygium polyglycoside compared with intravenous corticosteroids
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Not described

BDNF: brain-derived neurotrophic factor

CSF: cerebrospinal fluid

CSFF: cerebrospinal fluid filtration

GBS: Guillain-Barré syndrome

IFNb-1a: interferon beta-1a

IVIg: intravenous immunoglobulin

metHuBDNF: recombinant methionyl human brain-derived neurotrophic factor

RCT: randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ahuja 1980	Observational study of cyclophosphamide
Bos Eyssen 2011	This was a retrospective study of 54 mechanically ventilated people with GBS treated with selective decontamination of the digestive tract compared with 70 from other centres treated without. Non-randomised retrospective comparison. The method of selective decontamination of the digestive tract was not described
Colin-Jones 1965	Not in GBS. One person with CIDP treated with 6-mercaptopurine
Créange 1998	Not a RCT. Single case report of improvement following IFNb-1a. See text and Table 1
De Grandis 1995	Only 8 of 426 participants had GBS and their results were not described separately

(Continued)

Feasby 1991	Not a RCT. Three cases treated with muromonab-CD3. See text and Table 1
Francesconi 1972	No GBS cases included
Gamstorp 1966	Not in GBS. Single case of CIDP treated with 6-mercaptopurine
Garssen 2007	Non-randomised study of mycophenolate mofetil. See Summary of main results
Gorbunov 1995	RCT of pulsed versus continuous short-wave diathermy versus no treatment: not a pharmacological treatment
Hammond 1993	Only 15 participants had GBS and their results were not separately available in this randomised, double-blind, placebo-controlled trial of intravenous cefotaxime with amphotericin B, polymyxin E, and tobramycin applied to the oropharynx and enterally. There were altogether 40 participants with neurological diseases requiring intensive care. "There was no reduction in the incidence of infections (11 in the active group vs 10 in placebo) , and duration of ICU stay (30.1 +/- 22.5 vs 20.6 +/- 17.7 days) and hospital stay (49.3 +/- 31.9 vs 40 +/- 33.4 days) were unaffected as was the mortality (15 percent vs 15 percent)"
Hilz 1992	Not a RCT but a single case of a method for treating pressure sores
Huang L 1998	Ultraviolet irradiation. It is debatable whether this is a pharmacological treatment but in any case it could not be included because there was no description of randomisation or of time from onset when the ultraviolet irradiation was applied
Huang X 1998	Time when treatment given not stated. Treatment was ultraviolet irradiation. Allocation was said to be randomised but method unclear
Husstedt 1993	No GBS cases included in a study of ginkgo biloba extract
Li 1998	Not stated whether it was randomised. Ultraviolet irradiation. Time from onset differed between irradiation and control groups
Li 2007	A randomised trial of lymphoplasmapheresis versus supportive treatment alone in 66 participants: the treatment tested included plasma exchange which is the subject of another Cochrane review
Meythaler 2000	Treatment started more than 1 year after disease onset. Cross-over design RCT of 4-aminopyridine
Ostronoff 2008	Not RCT. Single case report of improvement following rituximab in 1 person with GBS following haematopoietic stem cell transplantation
Palmer 1965	Not in GBS. Single case of CIDP treated with 6 mercaptopurine
Palmer 1966	Not in GBS. Single case of CIDP treated with 6 mercaptopurine
Rosen 1976	Not RCT. Case series treated with cyclophosphamide. See Discussion and Table 1
Schaller 2001	Not RCT. Single case of GBS treated with IFN β -1a

(Continued)

Sendhilkumar 2013	Excluded because not a pharmacological treatment and not conducted in the acute phase (RCT of pranayama (yoga) and meditation in rehabilitation)
Umapathi 2014	Proposed RCT of azithromycin in GBS associated with diarrhoea. Not yet started or funded as at 1 March 20115 (personal communication from author)
Wang 2006	Not a pharmacological treatment, but acupuncture. 25 participants were randomised to electroacupuncture for 14 days and 24 to IVIg 0.4 g/kg daily for 5 days. Sequence generation was unclear, allocation concealment was done, blinding was not done, outcome data were complete, selective outcome reporting and other sources of bias were unclear. Mean improvement with acupuncture after 4 weeks was 1.58 (0.33) grades and with IVIg 1.68 (0.21) grades. Median (95% CI) time to unaided walking was 79.5 (58.7 to 100.3) and 81.2 (59.8 to 102.6) grades. There were no deaths. Adverse events were not described
Warembourg 1967	No GBS cases and not a RCT. See Discussion and Table 1
Yuill 1970	Not RCT. Single case report of use of azathioprine
Zagar 1995	Review not a RCT

CI: confidence interval

GBS: Guillain-Barré syndrome

RCT: randomised controlled trial

CIDP: chronic inflammatory demyelinating polyradiculoneuropathy

IFNb-1a: interferon beta-1a

IVIg: intravenous immunoglobulin

Characteristics of ongoing studies [ordered by study ID]

[Davidson 2014](#)

Trial name or title	Inhibition of complement activation (eculizumab) in Guillain-Barré syndrome study
Methods	Parallel-group RCT
Participants	30
Interventions	Ecuzumab, 900 mg intravenously once a week or placebo
Outcomes	Incidence of adverse and serious adverse events for 6 months; improvement of 1 or more grade in functional outcome (on the 6-point GBS disability scale) at 4 weeks
Starting date	September 2014
Contact information	ian.anderson2@ggc.scot.nhs.uk

Davidson 2014 (Continued)

Notes	-
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JET-GBS 2015

Trial name or title	JET-GBS - Japanese eculizumab trial for GBS
Methods	Prospective, multicentre, double-blind RCT
Participants	33 (estimated) participants with Guillain-Barré syndrome
Interventions	Eculizumab or placebo
Outcomes	Primary outcomes: Incidence of adverse and serious adverse events for 6 months; improvement of 1 or more grade in functional outcome (GBS disability grade scale) at 4 weeks
Starting date	July 2015
Contact information	sonoko.m@mb.infoweb.ne.jp
Notes	NCT02493725

GBS: Guillain-Barré syndrome

DATA AND ANALYSES

Comparison 1. IFNb-1a versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disability grade after 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Improvement by 1 or more grades after 4 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Participants with 1 or more serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. BDNF versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disability grade after 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Improvement in disability grade by one or more points after 4 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Death or disability after 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. CSF filtration versus plasma exchange

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disability grade after 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Improvement by 1 or more grades after 4 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Adverse events leading to cessation of treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Tripterygium polyglycoside versus corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disability grade by one or more points after 8 weeks	1	43	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.02, 2.11]
2 Adverse events	1	43	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [0.12, 66.75]

Analysis 1.1. Comparison 1 IFNb-1a versus placebo, Outcome 1 Improvement in disability grade after 4 weeks.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 1 IFNb-1a versus placebo

Outcome: 1 Improvement in disability grade after 4 weeks

Analysis 1.2. Comparison 1 IFNb-1a versus placebo, Outcome 2 Improvement by 1 or more grades after 4 weeks.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 1 IFNb-1a versus placebo

Outcome: 2 Improvement by 1 or more grades after 4 weeks

Analysis 1.3. Comparison 1 IFNb-1a versus placebo, Outcome 3 Death.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 1 IFNb-1a versus placebo

Outcome: 3 Death

Analysis 1.4. Comparison 1 IFNb-1a versus placebo, Outcome 4 Participants with 1 or more serious adverse events.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 1 IFNb-1a versus placebo

Outcome: 4 Participants with 1 or more serious adverse events

Analysis 2.1. Comparison 2 BDNF versus placebo, Outcome 1 Improvement in disability grade after 4 weeks.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 2 BDNF versus placebo

Outcome: 1 Improvement in disability grade after 4 weeks

Analysis 2.2. Comparison 2 BDNF versus placebo, Outcome 2 Improvement in disability grade by one or more points after 4 weeks.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 2 BDNF versus placebo

Outcome: 2 Improvement in disability grade by one or more points after 4 weeks

Analysis 2.3. Comparison 2 BDNF versus placebo, Outcome 3 Death.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 2 BDNF versus placebo

Outcome: 3 Death

Analysis 2.4. Comparison 2 BDNF versus placebo, Outcome 4 Death or disability after 12 months.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 2 BDNF versus placebo

Outcome: 4 Death or disability after 12 months

Analysis 2.5. Comparison 2 BDNF versus placebo, Outcome 5 Serious adverse events.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 2 BDNF versus placebo

Outcome: 5 Serious adverse events

Analysis 3.1. Comparison 3 CSF filtration versus plasma exchange, Outcome 1 Improvement in disability grade after 4 weeks.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 3 CSF filtration versus plasma exchange

Outcome: 1 Improvement in disability grade after 4 weeks

Analysis 3.2. Comparison 3 CSF filtration versus plasma exchange, Outcome 2 Improvement by 1 or more grades after 4 weeks.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 3 CSF filtration versus plasma exchange

Outcome: 2 Improvement by 1 or more grades after 4 weeks

Analysis 3.3. Comparison 3 CSF filtration versus plasma exchange, Outcome 3 Death.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 3 CSF filtration versus plasma exchange

Outcome: 3 Death

Analysis 3.4. Comparison 3 CSF filtration versus plasma exchange, Outcome 4 Serious adverse events.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 3 CSF filtration versus plasma exchange

Outcome: 4 Serious adverse events

Analysis 3.5. Comparison 3 CSF filtration versus plasma exchange, Outcome 5 Adverse events leading to cessation of treatment.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 3 CSF filtration versus plasma exchange

Outcome: 5 Adverse events leading to cessation of treatment

Analysis 4.1. Comparison 4 Tripterygium polyglycoside versus corticosteroids, Outcome 1 Improvement in disability grade by one or more points after 8 weeks.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 4 Tripterygium polyglycoside versus corticosteroids

Outcome: 1 Improvement in disability grade by one or more points after 8 weeks

Analysis 4.2. Comparison 4 Tripterygium polyglycoside versus corticosteroids, Outcome 2 Adverse events.

Review: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome

Comparison: 4 Tripterygium polyglycoside versus corticosteroids

Outcome: 2 Adverse events

ADDITIONAL TABLES

Table 1. Other treatments studied in case reports and case series

Reference	Regimen	Number treated	Results
Azathioprine			
Yuill 1970	125 mg/day	1	By 4 weeks: 1 improved By end of follow up: 1 had mild residual deficit Adverse events: none reported
Cyclophosphamide			
Ahuja 1980	100 mg/day route not stated	4	4 improved by 4 weeks 1 stopped because of diarrhoea
Rosen 1976	40 mg/kg IV total over 3 to 4 days	12 (3 other cases had CIDP)	By 4 weeks: 10 improved and 1 died By end of follow up: 3 died, 6 improved and 3 were not followed Adverse events (of all 15 cases including CIDP): 2 had pneumonia, 1 haematuria and 11 alopecia
Murine monoclonal antibody muromonab-CD3against CD3 antigen on T cells			

Table 1. Other treatments studied in case reports and case series (Continued)

Feasby 1991	5 mg muromonab-CD3 IV for 10 days (1 stopped treatment after 3 days because EBV infection diagnosed)	3	1 worse, 1 same and 1 improved by 4 weeks 1 developed aseptic meningitis
Selective gut decontamination (SDD)			
Bos Eyssen 2011	Selective decontamination of the digestive tract	54	Retrospective comparison with 70 not treated with selective decontamination of the gut. "The median duration of mechanical ventilation without SDD was 42 days (interquartile range, IQR 25-77 days) versus 29 days with SDD (IQR 17-45 days)." There was no difference in neurological recovery after 6 months from first symptoms. Ventilator-associated pneumonia occurred in 12% (95% CI 2 to 22%) in the treated cohort and in 47% (95% CI 35 to 59%) in the non-treated cohort

IV: intravenous

CI: confidence interval

EBV infection: Epstein Barr infection

CIDP: chronic inflammatory demyelinating polyradiculoneuropathy

APPENDICES

Appendix I. Cochrane Neuromuscular Specialised Register (CRS) search strategy

#1 MeSH DESCRIPTOR Guillain-Barre Syndrome [REFERENCE] [STANDARD]

#2 "Guillain Barre" [REFERENCE] [STANDARD]

#3 "acute polyradiculoneuritis" or "acute polyneuritis" [REFERENCE] [STANDARD]

#4 MeSH DESCRIPTOR Polyneuropathies [REFERENCE] [STANDARD]

#5 MeSH DESCRIPTOR Polyradiculoneuropathy [REFERENCE] [STANDARD]

#6 inflammatory NEAR neuropathy or inflammatory NEAR neuropathies [REFERENCE] [STANDARD]

#7 #1 or #2 or #3 or #4 or #5 or #6 [REFERENCE] [STANDARD]

#8 (#1 or #2 or #3 or #4 or #5 or #6) AND (INREGISTER) [REFERENCE] [STANDARD]

Appendix 2. CENTRAL (CRSO) search strategy

Search run on Mon Jan 25 2016

#1("guillain barre syndrome" or polyradiculoneuropathy or polyneuropathies):TI,AB,KY345
#2("acute polyradiculoneuritis" or "acute polyneuritis"):TI,AB,KY0
#3(inflammatory NEAR5 neuropath*):TI,AB,KY42
#4(inflammatory NEAR5 polyneuropathy*):TI,AB,KY55
#5("Acute motor axonal neuropathy"):TI,AB,KY2
#6#1 OR #2 OR #3 OR #4 OR #5393

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to January Week 2 2016>

Search Strategy:

1 randomized controlled trial.pt. (403450)
2 controlled clinical trial.pt. (89937)
3 randomized.ab. (300765)
4 placebo.ab. (154129)
5 clinical trials as topic.sh. (174283)
6 randomly.ab. (213171)
7 trial.ti. (130381)
8 or/1-7 (921852)
9 exp animals/ not humans.sh. (4173052)
10 8 not 9 (843868)
11 guillain barre syndrome.tw. or Guillain-Barre Syndrome/ (7027)
12 POLYRADICULONEUROPATHY/ or POLYNEUROPATHIES/ (8131)
13 (acute polyradiculoneuritis or acute polyneuritis).mp. (176)
14 (inflammatory adj5 neuropath\$3).tw. (1922)
15 (inflammatory adj5 polyneuropath\$3).tw. (1518)
16 Acute motor axonal neuropathy.tw. (227)
17 or/11-16 (15149)
18 10 and 17 (490)
19 review.pt. (1996933)
20 18 not 19 (310)
21 remove duplicates from 20 (310)

Appendix 4. EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2016 Week 04>

Search Strategy:

1 crossover-procedure.sh. (45701)
2 double-blind procedure.sh. (125477)
3 single-blind procedure.sh. (21354)
4 randomized controlled trial.sh. (390597)
5 (random\$ or crossover\$ or cross over\$ or placebo\$ or (doubl\$ adj blind\$) or allocat\$).tw.ot. (1213848)
6 trial.ti. (191246)
7 clinical trial/ (852129)
8 or/1-7 (1828993)
9 (animal/ or nonhuman/ or animal experiment/) and human/ (1433064)

10 animal/ or nonanimal/ or animal experiment/ (3471690)
 11 10 not 9 (2882305)
 12 8 not 11 (1717194)
 13 limit 12 to embase (1409903)
 14 Guillain Barre Syndrome/dt (2178)
 15 Guillain Barre syndrome/dt [Drug Therapy] (2178)
 16 Polyneuropathy/dt or Polyradiculoneuropathy/dt (1431)
 17 (guillain barre syndrome or acute polyradiculoneuritis or acute polyneuritis or Acute motor axonal neuropathy).tw. (8430)
 18 (inflammatory adj5 (neuropath\$3 or polyneuropath\$3)).tw. (4997)
 19 or/14-18 (14335)
 20 13 and 19 (1048)
 21 review/ (2053068)
 22 20 not 21 (667)
 23 remove duplicates from 22 (665)

Appendix 5. Clinical Trials Registries search strategy

Guillain-Barre syndrome

WHAT'S NEW

Last assessed as up-to-date: 18 January 2016.

Date	Event	Description
27 January 2016	New citation required but conclusions have not changed	No new completed trials. Two new ongoing trials. Background and discussion updated
27 January 2016	New search has been performed	Searches for CENTRAL and the Cochrane Neuromuscular Specialised Register were carried out using the new Cochrane software CRSO and CRS. Searches fully incorporated

HISTORY

Protocol first published: Issue 8, 2010

Review first published: Issue 3, 2011

Date	Event	Description
29 January 2013	New search has been performed	Searches updated to 28 August 2012
15 October 2012	New citation required but conclusions have not changed	Search updated. No new trials. One trial excluded. Selective digestive tract decontamination added to the

(Continued)

Discussion as a potential intervention

CONTRIBUTIONS OF AUTHORS

RACH wrote the first draft. All authors checked and edited subsequent drafts and approved the final version.

The Managing Editor of Cochrane Neuromuscular, Ruth Brassington, joined the review at this update. She independently assessed risk of bias in and data extraction from [Bensa 2000](#) and [Pritchard 2003](#), as two authors of this review (RACH and RDMH or JP) were investigators in each of these trials.

DECLARATIONS OF INTEREST

All three authors have conducted trials which were relevant for inclusion in this review.

JP was involved in the [Pritchard 2003](#) trial in this review, which was funded by Serono.

RACH's department received financial support for two trials included in this review, from Amgen for [Bensa 2000](#) and from Serono for [Pritchard 2003](#). Neither study showed a significant beneficial effect of the drug tested. More than eight years ago, RACH's department also received funding for trials in multiple sclerosis. RACH holds or has held consultancies with Baxter, CSL Behring, Grifols, LFB and Octapharma, all of which manufacture human immunoglobulin used in the treatment of GBS, but specifically excluded from this review. RACH holds or has held consultancies with BMS, Novartis and UCB, which are not known to him to be marketing or developing drugs for use in GBS. RACH serves as honorary board member of the GBS/CIDP Foundation International and medical patron of gain, charities which serve the interests of people with GBS.

RDMH has nothing to declare relating to the current review, but declares financial relationships with Baxter Healthcare Ltd (payment of nurse salary to department); Grifols (development of educational presentations, conference travel expenses); CSL Behring (advisory board membership, conference travel expenses, supply of clinical equipment); and Kent Institute of Medicine and Surgery (shareholder). He is a co-author of one of the studies included in the review, [Bensa 2000](#).

RB is Managing Editor of Cochrane Neuromuscular. She has no known conflicts of interest. She was not involved in the later stages of the editorial process other than as a review author.

Two review authors (RACH and RDMH) have declared relationships with commercial companies producing IVIg, which is used in the treatment of GBS. IVIg is explicitly excluded from the review and is not considered to be a competing intervention with any of the currently included interventions. Cochrane Neuromuscular is satisfied after consultation with the Funding Arbiter that these relationships do not represent a conflict of interest in this version of the review.

SOURCES OF SUPPORT

Internal sources

- None, UK.

External sources

- None, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The words 'change in', which had been inadvertently omitted in the protocol, were inserted in the review for the primary outcome: 'The primary outcome will be *change in* disability grade (Hughes 1978) four weeks after randomisation; we subsequently revised 'change in' to 'improvement in' for consistency with the first secondary outcome.

RB joined the review for this update.

The review authors checked personal databases for non-randomised cohort studies, case series and case reports, which were additional to the resources specified in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

*Tripterygium; Adrenal Cortex Hormones [therapeutic use]; Brain-Derived Neurotrophic Factor [*therapeutic use]; Cerebrospinal Fluid; Filtration; Guillain-Barre Syndrome [*drug therapy]; Immunoglobulins, Intravenous; Interferon beta-1a [therapeutic use]; Interferon-beta [*therapeutic use]; Plant Preparations [*therapeutic use]; Plasma Exchange; Randomized Controlled Trials as Topic

MeSH check words

Humans