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

Doets AY, Hughes RAC, Brassington R, Hadden RDM, Pritchard J

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

Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD008630.

DOI: [10.1002/14651858.CD008630.pub5](https://doi.org/10.1002/14651858.CD008630.pub5).

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Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for
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[Intervention Review]

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 (conclusions changed), published in Issue 1, 2020.

Citation: Doets AY, Hughes RAC, Brassington R, Hadden RDM, Pritchard J. Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain-Barré syndrome. *Cochrane Database of Systematic Reviews* 2020, Issue 1. Art. No.: CD008630. DOI: [10.1002/14651858.CD008630.pub5](https://doi.org/10.1002/14651858.CD008630.pub5).

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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 previously 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 28 October 2019, we searched the Cochrane Neuromuscular Specialised Register, CENTRAL, 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.

Data collection and analysis

We followed standard Cochrane methodology.

Main results

We found six trials of five different interventions eligible for inclusion in this review. The trials were conducted in hospitals in Canada, China, Germany, Japan and the UK, and included 151 participants in total. All trials randomised participants aged 16 years and older (mean or median age in the trials ranged from 36 to 57 years in the intervention groups and 34 to 60 years in the control groups) with severe GBS, defined by the inability to walk unaided. One trial also randomised patients with mild GBS who were still able to walk unaided. We identified two new trials at this update. The primary outcome measure for this review was improvement in disability grade four weeks after randomisation. Four of six trials had a high risk of bias in at least one respect.

We assessed all evidence for the outcome mean improvement in disability grade as very low certainty, which means that we were unable to draw any conclusions from the data. One RCT with 19 participants compared interferon beta-1a (IFN β -1a) and placebo. It is uncertain whether IFN β -1a improves disability after four weeks (mean difference (MD) -0.1; 95% CI -1.58 to 1.38; very low-certainty evidence). A trial with 10 participants compared brain-derived neurotrophic factor (BDNF) and placebo. It is uncertain whether BDNF improves disability after four weeks (MD 0.75; 95% CI -1.14 to 2.64; very low-certainty evidence). A trial with 37 participants compared cerebrospinal fluid (CSF) filtration and plasma exchange. It is uncertain whether CSF filtration improves disability after four weeks (MD 0.02; 95% CI -0.62 to 0.66; very low-certainty evidence). One trial that compared the Chinese herbal medicine tripterygium polyglycoside with corticosteroids with 43 participants did not report the risk ratio (RR) for an improvement by one or more disability grade after four weeks, but did report improvement after eight weeks. It is uncertain whether tripterygium polyglycoside improves disability after eight weeks (RR 1.47; 95% CI 1.02 to 2.11; very low-certainty evidence). We performed a meta-analysis of two trials comparing eculizumab and placebo with 41 participants. It is uncertain whether eculizumab improves disability after four weeks (MD -0.23; 95% CI -1.79 to 1.34; very low-certainty evidence). Serious adverse events were uncommon in each of the trials and evidence was graded as either low or very low. It is uncertain whether serious adverse events were more common with IFN β -1a versus placebo (RR 0.92, 95% CI 0.23 to 3.72; 19 participants), BDNF versus placebo (RR 1.00, 95% CI 0.28 to 3.54; 10 participants) or CSF filtration versus plasma exchange (RR 0.13, 95% CI 0.01 to 2.25; 37 participants). The trial of tripterygium polyglycoside did not report serious adverse events. There may be no clear difference in the number of serious adverse events after eculizumab compared to placebo (RR 1.90, 0.34 to 10.50; 41 participants). We found no clinically important differences in any of the outcome measures selected for this review in any of the six trials. However, sample sizes were small and therefore clinically important benefit or harm cannot be excluded.

Authors' conclusions

All six RCTs were too small to exclude clinically important benefit or harm from the assessed interventions. The certainty of the evidence was low or very low for all interventions and outcomes.

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 corticosteroids, intravenous immunoglobulin and plasma exchange for people with Guillain-Barré syndrome (GBS).

Background

GBS is an acute (sudden and severe), paralysing disease caused by inflammation of the nerves (damage that occurs due to the body's immune system). Symptoms reach their worst within four weeks of onset. Between 3% and 17% 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 (human antibodies harvested from blood donations given through a drip) can help speed up the recovery. Corticosteroids are probably not effective. Despite the use of plasma exchange or intravenous immunoglobulin many people with GBS have long-term disability. We need to find what other treatments have been tried as a basis for launching new trials.

Study characteristics

Cochrane Review authors collected and analysed all relevant randomised controlled trials (RCTs) to answer the review question. In RCTs people are allocated to treatment groups at random, which reduces bias. We found six eligible RCTs testing five different treatments in a total of 151 participants. We were uncertain about the evidence from the trials. One RCT with only 19 participants compared interferon beta-1a (a drug that is beneficial in multiple sclerosis) with placebo (a sham treatment). 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. A fifth trial with eight participants and a sixth with 34 participants compared eculizumab (a drug that blocks complement, a key inflammatory component) with placebo. Five trials received commercial company support. Support for the trial of the Chinese herbal medicine is unknown.

Key results and certainty 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 that 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 trial authors did not report other clinical outcomes. Serious adverse events were uncommon with each of the five treatments investigated in the identified trials and rates were not different from 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.

The evidence is up to date to October 2019.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Interferon beta-1a versus placebo for Guillain-Barré syndrome

Interferon beta-1a versus placebo for Guillain-Barré syndrome

Patient or population: people with Guillain-Barré syndrome

Settings: 4 UK hospitals

Intervention: interferon beta-1a (IFNb-1a)

Comparison: placebo

Outcomes		Illustrative comparative risks* (95% CI)		Relative ef- fect (95% CI)	No. of partic- ipants (RCTs)	Certainty of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		Placebo	IFNb-1a				
Improvement in disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead		The mean im- provement in disability grade after 4 weeks in the control group was 1.3 grades^a	The mean im- provement in dis- ability grade after 4 weeks in the in- tervention group was 0.1 grades lower (1.58 lower to 1.38 higher)		19 (1 RCT)	⊕⊕⊕⊕ Very low^{b,c}	It is uncertain whether IFNb-1a improves disability (defined by mean disability grade) after 4 weeks.
Improvement in disability grade Defined as achievement of a specified degree of improvement	Improvement by 1 or more disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead	500 per 1000	540 per 1000 (210 to 1000)	RR 1.08 (0.42 to 2.77)	19 (1 RCT)	⊕⊕⊕⊕ Very low^{b,c}	It is uncertain whether IFNb-1a improves disability (by ≥ 1 disability grade) after 4 weeks.
	Improvement by 6 or more points in I-RODS score after 4 weeks Assessed with: centile metric scale (0 to 100)	Not measured					

Time from randomisation until recovery of unaided walking (median, days (95% CI))	18 (11 to 70)	59 (16 to infinity)	-	19 (1 RCT)	⊕⊕⊕⊕ Very low ^{b,d}	It is uncertain whether IFNb-1a has an effect on the time from randomisation until recovery of unaided walking.
Time from randomisation until discontinuation of ventilation (for those ventilated)	Not measured					
Death	0 of 6 participants died in the control group	1 of 13 died in the IFNb-1a group	RR 1.50 (0.07 to 32.29)	19 (1 RCT)	⊕⊕⊕⊕ Low ^c	There may be no difference in the number of deaths after IFNb-1a compared to placebo.
Death or disability after 12 months	Not measured					
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 RCT)	⊕⊕⊕⊕ Very low ^{b,c}	It is uncertain whether IFNb-1a has an effect on the number of serious adverse events compared to placebo.

*The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aSince there is only one trial, we took the assumed risk to be that of the control group.

^bDowngraded once for trial limitations, as there was the potential for unblinding.

^cDowngraded twice for very serious imprecision. The confidence interval encompass potential benefit and potential harm.

^dDowngraded twice for very serious imprecision. The trial included only 19 participants, and confidence interval encompass a broad range of values.

Summary of findings 2. Brain-derived neurotrophic factor versus placebo for Guillain-Barré syndrome

Brain-derived neurotrophic factor versus placebo for Guillain-Barré syndrome

Patient or population: people with Guillain-Barré syndrome

Settings: 1 Canadian and 2 UK hospitals

Intervention: brain-derived neurotrophic factor (BDNF)

Comparison: placebo

Outcomes		Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		Placebo	BDNF				
Improvement in disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead		The mean improvement in disability grade after 4 weeks in the control group was 0.25^a	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 RCT)	⊕⊕⊕⊕ Very low^{b,c}	It is uncertain whether BDNF improves the disability grade after 4 weeks.
Improvement in disability grade Defined as achievement of a specified degree of improvement	Improvement by 1 or more disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead	500 per 1000	500 per 1000 (140 to 1000)	RR 1.00 (0.28 to 3.54)	10 (1 RCT)	⊕⊕⊕⊕ Very low^{b,c}	It is uncertain whether BDNF has an effect on improvement in disability (of ≥ 1 disability grades) after 4 weeks.
	Improvement by 6 or more points in I-RODS score after 4 weeks Assessed with: centile metric scale (0 to 100)	Not measured					
Time from randomisation until recovery of unaided walking, (median, days (95% CI))		84 (2 to infinity)	84 (4 to infinity)	-	10 (1 RCT)	⊕⊕⊕⊕ Very low^{c,d}	It is uncertain whether BDNF has an effect on the time from randomisation until recovery of unaided walking.

Time from randomisation until discontinuation of ventilation (for those ventilated) (median, weeks (range))	1 participant in the placebo group required mechanical ventilation, initiated during follow-up as a probable result of neurological deterioration. Ventilation was discontinued 4 weeks from randomisation	4 of 6 participants in the BDNF group were ventilated; median time to discontinuation was 12 weeks (12 weeks to infinity)	-	5 (1 RCT)	⊕⊕⊕⊕ Very low ^{c,e}	It is uncertain whether BDNF has an effect on the time from randomisation until discontinuation of ventilation, for those ventilated
Death	250 per 1000	168 per 1000 (15 to 1000)	RR 0.67 (0.06 to 7.85)	10 (1 RCT)	⊕⊕⊕⊕ Very low ^{b,c}	It is uncertain whether BDNF has an effect on the number of deaths compared to placebo.
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 RCT)	⊕⊕⊕⊕ Very low ^{b,c}	It is uncertain whether BDNF has an effect on death or disability after 12 months compared to placebo.
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 RCT)	⊕⊕⊕⊕ Very low ^{b,c}	It is uncertain whether BDNF has an effect on the number of serious adverse events compared to placebo.

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

BDNF: brain-derived neurotrophic factor; **CI:** confidence interval; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aWe used the control group to provide the assumed risk.

^bDowngraded twice for very serious imprecision. The trial included only 10 participants. Confidence interval encompass potential benefit and potential harm from brain-derived neurotrophic factor.

^cDowngraded once for risk of bias. Participants with brain-derived neurotrophic factor had more severe disease at randomisation and were randomised later.

^dDowngraded twice for very serious imprecision. The trial included only 10 participants, and confidence intervals encompass a broad range of values.

^eDowngraded twice for very serious imprecision. Only five participants were included in this analysis, and the range (weeks) is broad.

Summary of findings 3. Cerebrospinal fluid filtration versus plasma exchange for Guillain-Barré syndrome

Cerebrospinal fluid filtration versus plasma exchange for Guillain-Barré syndrome

Patient or population: people with Guillain-Barré syndrome

Settings: 1 German hospital

Intervention: cerebrospinal fluid (CSF) filtration

Comparison: plasma exchange

Outcomes		Illustrative comparative risks* (95% CI)		Relative ef- fect (95% CI)	No. of partic- ipants (RCTs)	Certainty of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		Plasma ex- change	CSF filtration				
Improvement in disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead		The mean im- provement in disability grade after 4 weeks in the control group was 0.8^a	The mean im- provement in disability grade after 4 weeks in the intervention group was 0.02 higher (0.62 lower to 0.66 higher)		37 (1 RCT)	⊕⊕⊕⊕ Very low^{b,c}	It is uncertain whether CSF filtration improves disability more than plas- ma exchange (defined by mean dis- ability grade) after 4 weeks.
Improvement in disability grade Defined as achievement of a specified degree of im- provement	Improvement by 1 or more disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead	500 per 1000	470 per 1000 (240 to 920)	RR 0.94 (0.48 to 1.84)	37 (1 RCT)	⊕⊕⊕⊕ Very low^{b,c}	It is uncertain whether CSF filtration improves disability more than plas- ma exchange (by ≥ 1 disability grade) after 4 weeks.
	Improvement by 6 or more points in I- RODS score after 4 weeks	Not measured					

Assessed with: centile metric scale (0 to 100)						
Time from randomisation until recovery of unaided walking (median, days (range))	90 (6 to 420)	42 (13 to 433)	-	37 (1 RCT)	⊕⊕⊕⊕ Very low ^{b,d}	It is uncertain whether CSF filtration has an effect on the time from randomisation until recovery of unaided walking.
Time from randomisation until discontinuation of ventilation (for those ventilated)	Not measured					
Death	50 per 1000	59 per 1000 (4 to 871)	RR 1.18 (0.08 to 17.42)	37 (1 RCT)	⊕⊕⊕⊕ Low ^c	There may be no difference in the number of deaths after CSF filtration compared to plasma exchange.
Death or disability after 12 months	Not measured					
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 RCT)	⊕⊕⊕⊕ Very low ^{b,c}	It is uncertain whether CSF filtration has an effect on the number of serious adverse events compared to plasma exchange.

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

CI: confidence interval; **CSF:** cerebrospinal fluid; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aWe took the assumed risk to be the risk in the plasma exchange group.

^bDowngraded once for trial limitations, as participants were not blinded.

^cDowngraded twice for very serious imprecision. Confidence interval encompassed the possibility of effects favouring cerebrospinal fluid filtration or plasma exchange.

^dDowngraded twice for very serious imprecision. The trial included only 37 participants, and confidence intervals encompass a broad range of values.

Summary of findings 4. Tripterygium polyglycoside versus corticosteroids for Guillain-Barré syndrome

Tripterygium polyglycoside versus corticosteroids for Guillain-Barré syndrome

Patient or population: people with Guillain-Barré syndrome
Settings: China
Intervention: tripterygium polyglycoside
Comparison: corticosteroids

Outcomes		Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
		Assumed risk	Corresponding risk				
		Corticosteroids	Tripterygium polyglycoside				
Improvement in disability grade after 4 weeks		Not measured					
Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead							
Improvement in disability grade	Improvement by one or more disability grade after 4 weeks ^a	619 per 1000 ^a	910 per 1000 (631 to 1000)	RR 1.47 (1.02 to 2.11)	43 (1 RCT)	⊕⊕⊕⊕ Very low ^{b,c,d}	It is uncertain whether Tripterygium polyglycoside has an effect on improvement in disability compared with corticosteroids (of ≥ 1 disability grades) after 8 weeks.
	Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead						
	In absence of data at 4 weeks, we report the outcome at 8 weeks						
	Improvement by 6 or more points in I-RODS score after 4 weeks	Not measured					
	Assessed with: centile metric scale (0 to 100)						
Time from randomisation until recovery of unaided walking		Not measured					
Time from randomisation until discontinuation of ventilation (for those ventilated)		Not measured					
Death		No deaths reported in this trial in either the tripterygium or corticosteroid groups		Not estimable	43 (1 RCT)	-	-

Death or disability after 12 months	Not measured				
Participants with 1 or more serious adverse events	Not reported	Not estimable	43 (1 RCT)	-	0 of 21 participants treated with corticosteroids experienced adverse events and 1 of 22 participants treated with tripterygium polyglycoside (gastrointestinal toxicity, of unclear severity)

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

CI: confidence interval; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aAssumed risk has been taken as that of the corticosteroid group.

^bPrimary outcome for this review was to be measured at 4 weeks but the only available data comes from 8 weeks (downgraded once for indirectness).

^cDowngraded once for trial limitations. The translator of the Chinese text classified the risk of bias as unclear. The trial compared oral tripterygium versus intravenous corticosteroids and was unblinded.

^dDowngraded once for serious imprecision. CI encompass the possibility of little or no effect from tripterygium polyglycoside and substantial benefit.

^eDowngraded twice for very serious imprecision. CI encompass the possibility of large differences between the treatment groups in either direction.

Summary of findings 5. Eculizumab versus placebo for Guillain-Barré syndrome

Eculizumab versus placebo for Guillain-Barré syndrome

Patient or population: adults with severe Guillain-Barré syndrome (GBS disability score > 2), within 2 weeks from onset

Setting: specialist hospitals

Intervention: eculizumab

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	Nº of participants (RCTs)	Certainty of the evidence (GRADE)	Comments
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	Risk with placebo	Risk with eculizumab				
Improvement in disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead	The mean improvement in disability grade after 4 weeks was 1.08^a	MD 0.23 lower (1.79 lower to 1.34 higher)	-	40 (2 RCTs)	⊕⊕⊕⊕ Very low^{b,c}	It is uncertain whether eculizumab improves disability grade after 4 weeks
Improvement in disability grade Defined as achievement of a specified degree of improvement	Improvement by one or more disability grade after 4 weeks Scale ranges from grade 0 to 6 where 0 is healthy and 6 is dead	Trial population ^d 692 per 1000	RR 0.85 (0.43 to 1.69)	40 (2 RCTs)	⊕⊕⊕⊕ Low^c	Ecuzumab may have no clear effect on improvement in disability (of ≥ 1 disability grades) after 4 weeks
	Improvement by 6 or more points in I-RODS score after 4 weeks Assessed with: centile metric scale (0 to 100)	Trial population ^d 769 per 1000	RR 0.91 (0.38 to 2.16)	40 (2 RCTs)	⊕⊕⊕⊕ Very low^{c,e}	It is uncertain whether ecuzumab affects the proportion of people with an improvement in disability (of ≥ 6 points in I-RODS score) after 4 weeks.
		588 per 1000 (298 to 1000)				
Time from randomisation until recovery of unaided walking (mean, weeks)	7.5 (SD 7.8)	8.5 (SD 6.4)	-	7 (1 RCT)	⊕⊕⊕⊕ Low^f	There may be no clear difference in the time from randomisation until recovery of unaided walking after ecuzumab compared to placebo.
Time from randomisation until discontinuation of ventilation (for those ventilated)	In one trial, the median time from randomisation until discontinuation of ventilation was shorter in the ecuzumab-treated group (18 days, 95% CI 11.0 to 31.0) than in the placebo group (34 days, 95% CI 27.0 to 41.0; P = 0.198). In this trial 4 participants in the ecuzumab group required ventilation, and 2 in the placebo group.		-	8 (2 RCTs)	⊕⊕⊕⊕ Very low^{g,h}	It is uncertain whether ecuzumab affects the time from randomisation until discontinuation of ventilation (for those ventilated), compared to placebo.

	In a second trial (N = 7), median time to discontinuation of ventilation in those ventilated (2 participants, both in the eculizumab group) was 102 days (range 20 days to 182 days).					
Death	Trial population ^d		RR 1.50 (0.08 to 26.86)	38 (2 RCTs)	⊕⊕○○ Low^c	There may be no clear difference in the number of deaths after eculizumab compared to placebo. The absence of any deaths in the control group prevented calculation of the absolute effect.
	0 deaths in the control group (11 participants)	1 death in the eculizumab group (27 participants)				
Death or disability after 12 months In the absence of data at 12 months, we report the outcome at 6 months	Trial population ^d		RR 1.21 (0.15 to 10.11)	38 (2 RCTs)	⊕○○○ Very low^{c,i}	It is uncertain whether eculizumab has an effect on death or disability after 6 months compared to placebo. This 6-month outcome was not one selected for this review - our protocol specified 12 months.
	91 per 1000	110 per 1000 (14 to 919)				
Participants with 1 or more serious adverse events	Trial population ^d		RR 1.90 (0.34 to 10.50)	41 (2 RCTs)	⊕⊕○○ Low^c	6 of 28 eculizumab participants had serious adverse events, of which 3 had a possible causal relationship to the trial drug. 1 of 13 control participants had a serious adverse event. There may be no clear difference in serious adverse events after eculizumab compared to placebo.
	77 per 1000	146 per 1000 (26 to 808)				

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RCT:** randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aBased on mean scores of control groups.

^bDowngraded once for inconsistency. I² statistic was 71%, which indicates substantial heterogeneity.

^cDowngraded twice for very serious imprecision. Confidence interval encompass important potential benefit and harm.

^dBased on overall event rate across control participants in both trials.

^eDowngraded once for inconsistency. I^2 statistic was 61%, which indicates substantial heterogeneity.

^fDowngraded twice for very serious imprecision. The trial included only seven participants, and the standard deviations are large.

^gDowngraded twice for very serious imprecision. Data were provided by eight ventilated participants in two trials.

^hDowngraded once for inconsistency as median times to discontinuation of ventilation differed substantially between the two trials.

ⁱDowngraded once for serious indirectness, as outcome at six months was provided instead of outcome at 12 months.

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 with GBS the disease is sufficiently severe to require the use of artificial ventilation (Van den Berg 2014; Willison 2016). Between 3% and 17% die during the first year after onset (Van den Berg 2013; Doets 2018). 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 Asia 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 2014; Hughes 2016; Chevret 2017). Plasma exchange and IVIg have reduced but not prevented prolonged stays in intensive care unit and hospital and long-term disability (Hughes 2014; Chevret 2017). Many people with GBS have persistent fatigue (Merkies 2016); 9% to 31% of people still require aid to walk one year after the onset of GBS (Rees 1998; Doets 2018), 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 (Simatos 2016), but it is likely that the need for improved pharmacological treatments will persist.

Guillain-Barré syndrome is thought to be caused by an aberrant immune response directed against the peripheral nerves resulting in damage to the myelin sheath or axonal membrane. Trials investigating the efficacy of pharmacological treatments other than corticosteroids, IVIg or plasma exchange have focused on inhibiting or modulating the immune response (interferon beta-1a (IFNβ-1a), tripterygium polyglycoside and eculizumab), neuroprotection and stimulation of axonal regeneration (brain-derived neurotrophic

factor), or novel techniques to remove pathogenic factors from the circulation (cerebrospinal fluid filtration; Bensa 2000; Zhang 2000; Wollinsky 2001; Pritchard 2003; ICA-GBS 2017; JET-GBS 2018).

How the intervention might work

Each intervention in this review had a different rationale. IFNβ-1a had been shown to have multiple beneficial effects and had been licensed for treatment in multiple sclerosis, an inflammatory disease of the central nervous system (Rice 2001). It reduced the severity of experimental autoimmune neuritis in an animal model of GBS (Zou 1999). Pritchard 2003 tested its efficacy in a pilot study in GBS.

Brain-derived neurotrophic factor (BDNF) is a trophic factor known to be important in the development of motor neurons, in people with GBS. Bensa 2000 tested it for GBS in a pilot study. Subsequently, experimental evidence emerged for a neuroprotective role of BDNF in mouse experimental allergic encephalomyelitis (Linker 2010).

Wollinsky 2001 developed a technique for removing, filtering and re-infusing the cerebrospinal fluid (CSF) with the aim of removing cells, bacteria, endotoxins, immunoglobulins, and inflammatory mediators that might be harmful. The theoretical basis was that inflammation of the spinal roots is important in the pathogenesis of GBS and that CSF filtration would remove 'blocking factors' that block nerve conduction (Brinkmeier 1992). However, the inflammation in GBS also affects the trunks and terminal portions of nerves (Feasby 2001), and the existence of 'blocking factors' has been questioned (Cummins 2003; Otto 2005).

Zhang 2000 undertook a RCT of tripterygium polyglycoside, an extract of the herb *Tripterygium wilfordii* (Thunder God Vine). It has been used as an anti-inflammatory agent in traditional Chinese medicine for many years. There are reports of it benefiting prevention of renal allograft rejection and treatment of Crohn's disease and rheumatoid arthritis (Goldbach-Mansky 2009). Tripterygium polyglycoside extracts contain 380 metabolites. The most active ingredients are terpenoids, some of which inhibit key pathways in T cell activation and cyclo-oxygenase and nitric oxide production (Goldbach-Mansky 2009).

Evidence from clinicopathological and animal model studies has indicated a role for the complement cascade as a terminal effector in the induction of nerve damage in GBS, which has increased the interest in complement factor inhibitors as potential therapeutic agents for GBS (Goodfellow 2016). Eculizumab, a humanised anti-C5 antibody, has already been shown to be effective in animal models for Miller Fisher syndrome in vivo and in vitro, and safe and effective in several other complement-mediated human diseases (Hillmen 2004; Halstead 2005; Halstead 2008; Fitzpatrick 2011; Legendre 2013). The safety and efficacy of eculizumab in people with GBS have now been assessed in two small RCTs that compared IVIg with eculizumab to IVIg and placebo, which have been included in this review (ICA-GBS 2017; JET-GBS 2018).

Why it is important to do this review

The treating doctor has a responsibility to know about the evidence for all treatments that 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. This is a further update of a review first published in 2011, and previously updated in 2013 and 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 eligible RCTs or quasi-RCTs (using alternate or other systematic allocation) identified by the searches. The rationale to include quasi-randomised trials was based on the rarity of GBS and the knowledge that few RCTs had been performed. In fact we discovered no quasi-randomised trials. As anticipated, during the search for RCTs we also identified trials of pharmacological treatments that had not been subjected to randomised trials, including cohort studies, case reports and case series, which we addressed in the [Agreements and disagreements with other studies or reviews](#) section of the Discussion. We did not include non-randomised studies in the Results and only noted them if 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. We might have missed (and therefore have not included) some non-randomised studies because there is no method for searching systematically that would have identified all such studies. Although not planned in the protocol, we also searched our personal databases for non-randomised trials.

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 published reports of the included treatment trials never distinguished between the two forms. We included trials that did not conform exactly to these criteria provided that the trial 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 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.

The minimum clinically important difference of change in average GBS disability grade has never been calculated but a half grade has been arbitrarily defined as the amount that would be clinically important ([Plasma 1997](#)).

Secondary outcomes

- Improvement by one or more GBS disability grades after four weeks
- Improvement by six or more centile points in the Inflammatory Rasch-built Overall Disability Scale (I-RODS; [Draak 2014](#)) after four weeks
- Time from randomisation until recovery of unaided walking
- Time from randomisation until discontinuation of ventilation (for those ventilated)
- Death
- Death or disability (inability to walk without aid) after 12 months
- Serious adverse events (that is adverse events that are life-threatening or fatal, or require or prolong hospital stay).

Search methods for identification of studies

Electronic searches

On 28 October 2019, we searched the following databases:

- Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies (CRS-Web; [Appendix 1](#));
- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 10) via the Cochrane Register of Studies (CRS-Web; [Appendix 2](#));
- MEDLINE (1946 to 25 October 2019; [Appendix 3](#));
- Embase (1974 to 25 October 2019; [Appendix 4](#)).

We also searched the following trials registries:

- www.clinicaltrials.gov (Appendix 5) on 17 October 2019;
- WHO trials registry (ICTRP; apps.who.int/trialsearch/) on 4 November 2019.

Searching other resources

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. 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 (RACH and RDMH or JP or AD) checked titles and abstracts identified by the search and decided independently which should be studied further. We obtained the full text of all trials selected as being potentially relevant. Two review authors (RACH and RDMH or JP or AD) 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 trials in the [Discussion](#).

Data extraction and management

Two review authors (RACH, and RDMH or JP or AD) independently extracted data on characteristics of included trials and trials outcomes and entered this information 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 trials that involved two review authors as trial authors, two other review authors (RB and AD), who had not been involved in the trials, 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, and RDMH or JP or AD) independently assessed the risk of bias in each identified RCT using specially designed forms, using the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). A third review author (RB) independently assessed risk of bias and data extraction for [Bensa 2000](#) and [Pritchard 2003](#) as these trials involved two review authors as trial authors. We considered the following attributes: sequence generation, allocation concealment, blinding of participants and medical personnel, blinding of outcome assessment, 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 review author.

Measures of treatment effect

For dichotomous outcomes, such as 'improvement by one or more GBS disability grade after four weeks', we used Review Manager 5 (Review Manager 2014), to calculate a risk ratio (RR). For continuous outcomes we tested the significance of the difference between each pharmacological treatment and placebo, no treatment or other treatments by calculating the mean difference (MD). This method of calculating the outcome is a more sensitive measure than change in proportions of participants improved. We expressed uncertainty with 95% confidence intervals (CIs). For time-to-event measures we used the median (95% CI), median (range) or mean (standard deviation (SD)), depending on how the data were presented in the trials.

Unit of analysis issues

If in future we identify trials where multiple trial arms are reported in a single trial, we will include only the treatment arms relevant to the review topic. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will follow guidance in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* to avoid double-counting (Higgins 2011b). Our preferred approach will be to halve the control group.

Dealing with missing data

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

Assessment of heterogeneity

Where there were multiple trials of one intervention and evidence of significant heterogeneity between trials had been detected using the I^2 statistic (Higgins 2003), we sought explanations for the heterogeneity.

We planned to use the rough guide to interpretation as outlined in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We avoided the use of absolute cut-off values, but interpreted the I^2 statistic in relation to the size and direction of effects and strength of evidence for heterogeneity (e.g. P value from the χ^2 test, or CI for I^2 statistic; Deeks 2011).

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

We conducted a meta-analysis using the data from the two eculizumab trials, where we calculated a pooled treatment effect across trials using [Review Manager 2014](#).

We used a random-effects model in [Review Manager 2014](#), as this is usually a more conservative approach and carried out a sensitivity analysis using a fixed-effect model.

Summary of findings and assessment of the certainty of the evidence

We 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 (trial limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of a body of evidence (trials that contribute data for the prespecified outcomes), according to methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2011a](#); [Schünemann 2011b](#)). We based decisions on downgrading for imprecision due to small trial size on the 95% CIs, which is considered a reasonable approach in rare diseases. We would have resolved disagreements by discussion or by involving another review author. We considered RCTs as high-certainty evidence if the five factors above were not present to any serious degree, but downgraded the certainty to moderate, low or very low if any of them were present. We downgraded the certainty of the evidence once if a GRADE consideration was serious and twice if very serious. We used GRADEpro GDT software to prepare the tables ([GRADEpro GDT](#)). Using our assessments we drew conclusions about the certainty 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 trials.

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

- 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).
- Participants having or not having a documented relevant sensory deficit on routine neurological examination at randomisation (symptoms alone would have been ignored).
- Participants having or not having a history of diarrhoea (gastroenteritis) within the six weeks before the onset of neuropathic symptoms.
- 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).
- 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. We compared random-effects and fixed-effect analyses.

RESULTS

Description of studies

Results of the search

The previous versions of this review included four completed RCTs. Our new database search for this update yielded 467 records and we found an additional record in the WHO International Clinical Trials Registry Platform. After deduplication, we screened 368 references. Thirty-six were already listed in the review; we therefore screened 332 records and excluded 319, which were not relevant or not RCTs. We assessed 13 full-text articles for eligibility. We included two new RCTs (previously identified as ongoing), each of eculizumab in severe GBS ([ICA-GBS 2017](#); [JET-GBS 2018](#)). These accounted for 12 references. We excluded a third trial, of hyperbaric oxygen and acupuncture in children because of lack of clear evidence of randomisation ([Ding 2015](#)). [Figure 1](#) illustrates the trial selection process.

Figure 1. Study flow diagram

ClinicalTrials.gov included an open, non-randomised, phase I trial of cord blood regulatory T cells that has not yet been started ([NCT03773328](#)), an open-label, single-arm, phase I trial of a C1q inhibitor that has started recruitment ([NCT04035135](#)), and an open-label, single-arm, multicenter, phase II trial of imlifidase, an immunoglobulin G (IgG)-degrading enzyme, that has also started recruitment ([NCT03943589](#)). We did not identify any ongoing RCTs or quasi-randomised trials during our searches.

Included studies

We included four small, randomised, placebo-controlled, double-blind trials, one of IFN β -1a ([Pritchard 2003](#)), one of brain-derived neurotrophic factor (BDNF) ([Bensa 2000](#)), and two phase II clinical trials of the complement inhibitor eculizumab ([ICA-GBS 2017](#); [JET-GBS 2018](#)). We also included two trials that were not double-blind: 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](#)). The trials included a total of 151 participants with acute GBS aged 16 years or more.

Disease severity at randomisation was severe, defined as the inability to walk unaided, in all the trials, except that [Zhang 2000](#) also included participants who were still able to walk unaided. Included participants came from hospitals in the UK, Canada, China, Germany and Japan. The funding source of [Zhang 2000](#) is not known. The other trials were all investigator-led but either the trial was funded by a drug company ([Bensa 2000](#); [ICA-GBS 2017](#); [Pritchard 2003](#)), or the intervention was paid for by a pharmaceutical company ([JET-GBS 2018](#); [Wollinsky 2001](#)).

Excluded studies

We excluded 32 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. We reported non-randomised trials of pharmacological treatments

for GBS with sufficient description of the diagnosis, treatment, and pretreatment and outcome disability grade in both the [Characteristics of excluded studies](#) and the [Discussion](#). These included one historically-controlled trial of mycophenolate mofetil ([Garssen 2007](#)), and other non-randomised case series or case reports of other agents ([Bos Eyssen 2011](#); [Hammond 1993](#)). We reported other excluded studies only in [Characteristics of excluded studies](#).

Studies awaiting assessment

There are no trials to report that are awaiting assessment.

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](#).

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bensa 2000	+	+	+	+	+	+	-
ICA-GBS 2017	+	+	+	+	+	+	+
JET-GBS 2018	+	+	+	+	+	+	+
Pritchard 2003	+	+	+	-	+	+	+
Wollinsky 2001	+	-	?	-	-	+	-
Zhang 2000	?	?	-	-	?	?	?

The very small trials of IFNb-1a (Pritchard 2003) and BDNF (Bensa 2000) had a high risk of bias for blinding of outcome assessment and baseline imbalance, respectively but were otherwise at low risk of bias.

The trial of CSF filtration had a high risk of bias for allocation concealment, blinding of outcome assessment and other bias (from individual analysis issues), an unclear risk of bias for blinding of participants and medical personnel, and a low risk of bias for random sequence generation and selective outcome reporting (Wollinsky 2001).

The trial of tripterygium polyglycoside had a high risk of bias for blinding of medical personnel, participants and outcome assessors and an unclear risk of bias in other domains (Zhang 2000).

Both eculizumab trials were at low risk of bias in all respects (ICA-GBS 2017; JET-GBS 2018).

Effects of interventions

See: [Summary of findings for the main comparison Interferon beta-1a versus placebo for Guillain-Barré syndrome](#); [Summary of](#)

findings 2 Brain-derived neurotrophic factor versus placebo for Guillain-Barré syndrome; **Summary of findings 3** Cerebrospinal fluid filtration versus plasma exchange for Guillain-Barré syndrome; **Summary of findings 4** Tripterygium polyglycoside versus corticosteroids for Guillain-Barré syndrome; **Summary of findings 5** Eculizumab versus placebo for Guillain-Barré syndrome

Interferon beta-1a versus placebo

One small RCT (Pritchard 2003), with a low risk of bias other than that for blinding (see Figure 2; Characteristics of included studies; 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). 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.

Primary outcome: improvement in disability grade four weeks after randomisation

The mean improvement in disability grade (Hughes 1978), after four weeks was 1.2 grades (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 of a grade less improvement in the IFNb-1a group (MD -0.10, 95% CI -1.58 to 1.38; 1 RCT, 19 participants; very low-certainty evidence; Analysis 1.1).

Secondary outcomes

Improvement by one or more GBS disability grade after four weeks

Correspondingly, the RR of improvement by one or more GBS disability grades after four weeks was 1.08 in favour of IFNb-1a (95% CI 0.42 to 2.77; 1 RCT, 19 participants; very low-certainty evidence; Analysis 1.2).

Improvement by six or more centile points in the Inflammatory Rasch-built Overall Disability Scale (I-RODS) after four weeks

Pritchard 2003 predated I-RODS (Draak 2014).

Time from randomisation until recovery of unaided walking

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 (1 RCT, 19 participants; very low-certainty evidence).

Time from randomisation until discontinuation of ventilation (for those ventilated)

Pritchard 2003 did not measure this outcome.

Death

The RR for death was 1.50 greater in the IFNb-1a group (95% CI 0.07 to 32.29; 1 RCT; 19 participants; low-certainty evidence; Analysis 1.3).

Death or disability (inability to walk without aid) after 12 months

Pritchard 2003 did not measure this outcome.

Serious adverse events

The RR for having one or more serious adverse events was 0.92 (95% CI 0.23 to 3.72; 1 RCT, 19 participants; very low-certainty evidence), and thus was slightly lower in the IFNb-1a group (Analysis 1.4).

Other outcome measures

None of the other differences in selected outcome measures reported by the trial authors, listed in the Included studies, was significantly different.

Pritchard 2003 was much too small to exclude clinically important benefit or harm from IFNb-1a.

Brain-derived neurotrophic factor versus placebo

One very small RCT (Bensa 2000), with a low risk of bias in all domains except for other bias (see Figure 2; Characteristics of included studies; Summary of findings 2), randomised six participants with severe early GBS to BDNF (four disability grade 5 and two grade 4) and four to placebo (all grade 4). 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.

Primary outcome: improvement in disability grade four weeks after randomisation

The mean improvement in disability grade (Hughes 1978) after four weeks was 1.0 grade (SD 1.1) in the BDNF group and 0.25 grade (SD 1.71) in the placebo group, thus resulting in 0.75 of a grade more improvement in the BDNF group than in the placebo group (95% CI -1.14 to 2.64; 1 RCT, 10 participants; very low-certainty evidence; Analysis 2.1).

Secondary outcomes

Improvement by one or more GBS disability grade after four weeks

The RR for improvement by one or more GBS disability grade after four weeks was the same in both groups (RR 1.00, 95% CI 0.28 to 3.54; 1 RCT, 10 participants; very low-certainty evidence; Analysis 2.2).

Improvement by six or more centile points in the Inflammatory Rasch-built Overall Disability Scale (I-RODS) after four weeks

Bensa 2000 predated I-RODS (Draak 2014).

Time from randomisation until recovery of unaided walking

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 (10 participants; very low-certainty evidence).

Time from randomisation until discontinuation of ventilation (for those ventilated)

Four of six (67%) participants in the BDNF group and one of four (25%) participants in the placebo group required mechanical ventilation during follow-up. Median times (range) from randomisation until discontinuation of ventilation were estimated from Figure 1 in the paper. Median time to discontinuation of ventilation for the participants in the BDNF

group was 12 weeks (range 12 weeks to infinity). The participant in the placebo group required mechanical ventilation during follow-up as a probable result of neurological deterioration, and this was discontinued after four weeks from randomisation (N = 5; very low-certainty evidence).

Death

The RR for death was lower in the BDNF group (RR 0.67, 95% CI 0.06 to 7.85; 1 RCT, 10 participants; very low-certainty evidence; [Analysis 2.3](#)).

Death or disability (inability to walk without aid) after 12 months

The RR for death or disability after 12 months was greater with BDNF than with placebo (RR 1.33, 95% CI 0.17 to 10.25; 1 RCT; 10 participants; very low-certainty evidence; [Analysis 2.4](#)).

Serious adverse events

In the BDNF group, three of six participants experienced serious adverse events, in comparison to two of four participants in the placebo group (RR 1.00, 95% CI 0.28 to 3.54; 1 RCT, 10 participants; very low-certainty evidence; [Analysis 2.5](#)).

Other outcome measures reported

[Bensa 2000](#) did not report any significant differences for the disability grade and arm grade at any of the follow-up assessments. Other prespecified outcome measures included the Medical Research Council (MRC) sum score, time taken to walk 10 m, grip strength, vital capacity and haematology, clinical chemistry and urine analysis, but [Bensa 2000](#) did not provide results for these measures ([Included studies](#)).

[Bensa 2000](#) was much too small to exclude clinically important benefit or harm from BDNF.

Cerebrospinal fluid filtration versus plasma exchange

One RCT ([Wollinsky 2001](#)), with a high risk of bias (see [Figure 2](#); [Characteristics of included studies](#); [Summary of findings 3](#)), compared 17 participants 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. 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 had disability grade 4 at randomisation. The outcomes selected for this review showed no significant differences between the groups.

Primary outcome: improvement in disability grade four weeks after randomisation

The mean improvement in disability grade ([Hughes 1978](#)) after four weeks was almost equal in the CSF filtration and the plasma exchange groups (MD 0.02, 95% CI -0.62 to 0.66; 1 RCT, 37 participants; very low-certainty evidence; [Analysis 3.1](#)).

Secondary outcomes

Improvement by one or more GBS disability grade after four weeks

Similarly, the number of participants with one or more grade of improvement after four weeks was almost equal in both groups (RR

0.94; 95% CI 0.48 to 1.84; 1 RCT, 37 participants; very low-certainty evidence; [Analysis 3.2](#)). These CIs were consistent with either a halving or almost doubling of the number.

Improvement by six or more centile points in the Inflammatory Rasch-built Overall Disability Scale (I-RODS) after four weeks

[Wollinsky 2001](#) predated I-RODS ([Draak 2014](#)).

Time from randomisation until recovery of unaided walking

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 at different times. 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 trial authors commented that the times were similar in both groups (37 participants; very low-certainty evidence).

Time from randomisation until discontinuation of ventilation (for those ventilated)

[Wollinsky 2001](#) did not measure this outcome.

Death

There was one death in each group resulting in a RR of 1.18 in favour of the plasma exchange group (95% CI 0.08 to 17.42; 1 RCT, 37 participants; low-certainty evidence; [Analysis 3.3](#)).

Death or disability (inability to walk without aid) after 12 months

[Wollinsky 2001](#) did not measure this outcome.

Serious adverse events

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; 1 RCT; 37 participants; very low-certainty evidence; [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; 1 RCT, 37 participants; very low-certainty evidence; [Analysis 3.5](#)).

Other outcome measures reported

We found no important differences in the other outcomes measured by the trial authors and listed in the [Included studies](#).

The small sample sizes in [Wollinsky 2001](#) prevent us from 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 ([Zhang 2000](#)), with an unclear risk of bias except for blinding, which was at high risk (see [Figure 2](#); [Characteristics of included studies](#); [Summary of findings 4](#)), compared 22 participants treated with the Chinese herbal medicine tripterygium polyglycoside (randomisation disability grade 2 in six participants, grade 3 in 12 participants and grade 4 in four participants) with 21 participants treated with high-dose corticosteroids (randomisation

disability grade 2 in seven participants, grade 3 in 11 participants and grade 4 in three participants).

Primary outcome: improvement in disability grade four weeks after randomisation

Zhang 2000 did not report improvement in disability grade (Hughes 1978) four weeks after randomisation, but after eight weeks 20 of 22 participants treated with tripterygium polyglycoside had improved by one or more GBS disability grade compared with 13 of 21 treated with high-dose corticosteroids: RR 1.47 (95% CI 1.02 to 2.11; 1 RCT, 43 participants; very low-certainty evidence; Analysis 4.1).

Secondary outcomes

Adverse events

Zhang 2000 reported only one adverse event: gastrointestinal toxicity in one person treated with tripterygium polyglycoside (RR 2.87, 95% CI 0.12 to 66.75; 1 RCT, 43 participants; very low-certainty evidence; Analysis 4.2).

Zhang 2000 did not measure other clinical outcomes nor the outcomes for this review.

Ecuzumab versus placebo

Two trials investigated ecuzumab in comparison to placebo (ICA-GBS 2017; JET-GBS 2018).

ICA-GBS 2017 had a low risk of bias (Figure 2; Characteristics of included studies; Summary of findings 5). The trial was funded by the company that produced the drug. It randomised eight participants with acute GBS and who were unable to walk independently to ecuzumab (five participants, mean disability grade 4) or placebo (three participants, mean disability grade 4). Ecuzumab or placebo was provided intravenously once weekly for the first four weeks. Additionally, all participants were treated with a standard course of IVIg (0.4 g/kg/day for five days) and ciprofloxacin either 400 mg oral or 500 mg intravenously once weekly for the first 10 weeks. The trial had a 26-week follow-up period. JET-GBS 2018 had similar inclusion and exclusion criteria and trial protocol to ICA-GBS 2017 (Characteristics of included studies). Ecuzumab or placebo was provided intravenously once weekly for the first four weeks, with standard IVIg treatment and antibiotic prophylaxis. Antibiotic prophylaxis was continued until eight weeks after the last trial drug administration. Twenty-three participants were randomised to receive ecuzumab (mean disability grade at baseline 3.9), and 11 to receive placebo (mean disability grade 4.0). The trial had a 24-week follow-up period.

Primary outcome: improvement in disability grade four weeks after randomisation

After four weeks, the mean difference in disability grade (Hughes 1978) was -0.23 (95% CI -1.79 to 1.34; $I^2 = 71\%$; 2 RCTs, 40 participants; very low-certainty evidence) in favour of the placebo group (Analysis 5.1; Figure 3).

Figure 3. Forest plot of comparison: 5 Ecuzumab versus placebo, outcome: 5.1 Improvement in disability grade after 4 weeks.

Secondary outcomes

Improvement by one or more GBS disability grade after four weeks

Seventeen of 27 participants in the ecuzumab group and nine of 13 participants in the placebo group had improved by at least one disability grade after four weeks (RR 0.85, 95% CI 0.43 to 1.69; $I^2 = 36\%$; 2 RCTs, 40 participants; low-certainty evidence; Analysis 5.2).

Improvement by six or more centile points in the Inflammatory Rasch-built Overall Disability Scale (I-RODS) after four weeks

Both trials also recorded the Inflammatory Rasch-built Overall Disability Scale (I-RODS) scores for all participants (Draak 2014). Both defined a clinically relevant improvement as an improvement of 6 or more points on the centile metric scale (Van Nes 2011). After four weeks, the RR of a clinically relevant improvement on the I-RODS was 0.91 (95% CI 0.38 to 2.16; $I^2 = 61\%$; 2 RCTs, 40 participants; very low-certainty evidence) in favour of the placebo group (Analysis 5.3).

Time from randomisation until recovery of unaided walking

Only ICA-GBS 2017 provided mean time from randomisation until recovery of unaided walking and was 8.5 (SD 6.4) weeks in the ecuzumab group and 7.5 (SD 7.8) weeks in the placebo group (7 participants; low-certainty evidence).

Time from randomisation until discontinuation of ventilation (for those ventilated)

In ICA-GBS 2017, two of five participants in the ecuzumab group needed mechanical ventilation, while neither of the participants in the placebo group were mechanically ventilated. The median time from randomisation until discontinuation of ventilation was 102 days (range 20 days to 182 days). In JET-GBS 2018, four of 23 participants in the ecuzumab group and two of 11 participants in the placebo group needed mechanical ventilation. The median time from randomisation until discontinuation of ventilation was shorter in the group treated with ecuzumab (18 days, 95% CI 11.0 to 31.0) than in the group treated with placebo (34 days, 95% CI 27.0 to 41.0). The P value was 0.198 (8 participants; very low-certainty evidence).

Death

Only one participant died. This participant had been treated with eculizumab: the death occurred from sepsis at week 21 and was not deemed due to the trial drug (ICA-GBS 2017). The RR of death was 1.50 (higher with eculizumab than placebo) but with very wide CI (95% CI 0.08 to 26.86, 2 RCTs, 38 participants; low-certainty evidence; Analysis 5.4).

Death or disability (inability to walk without aid) after 12 months

In absence of data for follow-up after one year, we have reported outcomes after six months. At that time, the difference in mean change in disability grade was 0.75 of a grade less improvement in the eculizumab group (95% CI -3.88 to 2.37; $I^2 = 87\%$; 2 RCTs, 38 participants; Analysis 5.5). Correspondingly, 24 of 27 participants in the eculizumab group had improved by at least one disability grade compared with 10 of 11 in the placebo group, RR 1.03 (95% CI 0.78 to 1.36; $I^2 = 6\%$; 2 RCTs, 38 participants; Analysis 5.6).

Both trials also reported the I-RODS scores after six months, which showed an improvement of at least 6 centile points on the I-RODS for all participants (11 of 11) in the placebo group and for 25 of 26 participants in the eculizumab group (RR 0.99, 95% CI 0.83 to 1.17; $I^2 = 0\%$; 2 RCTs, 37 participants; Analysis 5.7).

Four of 27 participants in the eculizumab group and one of 11 participants in the placebo group were either not able to walk independently or were dead after six months (RR 1.21, 95% CI 0.15 to 10.11; $I^2 = 23\%$; 2 RCTs, 38 participants; very low-certainty evidence; Analysis 5.8).

Serious adverse events

All the participants in both the eculizumab and the placebo groups had adverse events (RR 1.00, 95% CI 0.88 to 1.14; $I^2 = 0\%$; Analysis 5.9). Participants on eculizumab were possibly more likely to have serious adverse events than those on placebo: RR 1.90, 95% CI 0.34 to 10.50; $I^2 = 0\%$; 2 RCTs, 41 participants; low-certainty evidence; Analysis 5.10). Participants with serious adverse events with a possible causal relationship to the trial drug were one with a lower respiratory tract infection that prevented trial drug administration in ICA-GBS 2017, and one with anaphylaxis and another with an intracranial abscess following a haemorrhage in JET-GBS 2018.

Heterogeneity

We found a high level of heterogeneity for Analysis 5.1, Analysis 5.3, and Analysis 5.5. Both trials used the same trial protocol and intervention, but we identified some differences in participant characteristics between the two trial populations that might have contributed to this heterogeneity, including the geographic location, antecedent illness, electrophysiological subtypes and presence of anti-ganglioside antibodies. We did not perform a subgroup analysis because of the small numbers that would have been included in each of the subgroups.

Sensitivity analyses

Table 1 shows a sensitivity analysis comparing random-effects and fixed-effect models. For most analyses, we found similar results with both approaches. However, for improvement on the I-RODS after four weeks and for mean improvement in disability grade after six months we found a reverse effect when we compared the fixed-effect to the random-effects approach. After four weeks, the RR of improvement by 6 or more centile points on the I-RODS was 1.07

(95% CI 0.75 to 1.54) with a fixed-effect model, and 0.91 (95% CI 0.38 to 2.16) with a random-effects model. After six months, the mean improvement in disability grade with a fixed-effect approach was 0.24 grade (95% CI -0.55 to 1.03) more in the eculizumab group than in the placebo group, while this was 0.75 grade (95% CI -3.88 to 2.37) less with a random-effects approach (Table 1). However, differences between the treatment groups were still not significant and the CIs encompass the possibility of clinically important differences in either direction. Furthermore, the level of heterogeneity was the same with either approach.

Other outcome measures

No clinically meaningful differences were reported in the other outcomes listed in the Included studies, except for the proportion of participants that were able to run at week 24 in JET-GBS 2018. Seventeen of 23 participants in the eculizumab group were able to run after 24 weeks compared to two of 11 in the placebo group ($P = 0.004$; JET-GBS 2018).

Due to the small sample sizes results were very imprecise. Therefore, a clinically important benefit or harm from eculizumab cannot be excluded.

DISCUSSION

Summary of main results

This review identified and analysed six small RCTs investigating five different interventions in a total of 151 participants: each provided only very low- or low-certainty evidence. In a trial with 19 participants comparing IFN β -1a with placebo there was no clinically meaningful difference in improvement in disability grade after four weeks (Pritchard 2003). In a trial with 10 participants comparing BDNF with placebo, on average there was more improvement in disability grade after four weeks with BDNF, but the results were also consistent with much more or much less improvement (Bensa 2000). In a trial with 37 participants, there was no clinically meaningful difference between plasma exchange and CSF filtration in improvement in disability grade after four weeks (Wollinsky 2001). In a trial comparing the Chinese herbal medicine tripterygium polyglycoside with high-dose corticosteroids, the primary outcome for this review was not available but those receiving tripterygium polyglycoside possibly had more improvement in disability grade after eight weeks (Zhang 2000). The 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, so a possible beneficial effect of tripterygium polyglycoside was more likely (Hughes 2016). In two trials with altogether initially 42 participants comparing eculizumab with placebo, there was no clinically meaningful difference in improvement in disability grade after four weeks (ICA-GBS 2017; JET-GBS 2018). Furthermore, we did not find clinically important differences in any of the secondary outcome measures selected for this review in any of the six trials. However, sample sizes were small and therefore clinically important benefit or harm cannot be excluded.

Overall completeness and applicability of evidence

The evidence from published RCTs is likely to be complete because we have made use of Cochrane methods to search the literature. The evidence from the case studies and series described below cannot be complete since there is no known search strategy that will detect all published non-randomised trials.

Certainty of the evidence

We graded the certainty of the evidence from the RCTs as either low or very low due to:

- the very small number of participants randomised in all trials resulting in either serious or very serious imprecision;
- trial limitations including risk of bias due to the potential for unblinding (Pritchard 2003), an unblinded trial design (Wollinsky 2001; Zhang 2000), or baseline imbalances in disease severity (Bensa 2000); and
- inconsistency across trials resulting in substantial heterogeneity (ICA-GBS 2017; JET-GBS 2018).

Need for more trials

The long duration of illness, severe persistent disability and continued mortality from GBS emphasise the need for better treatments. Existing treatments with IVIg and plasma exchange are partially effective (Willison 2016). Where these are available, it is unethical to compare new treatments against placebo. The evidence in this systematic review is of such low certainty that it does not establish whether any of the treatments reviewed are beneficial or harmful. This emphasises the dearth of evidence on treatments other than IVIg, plasma exchange and corticosteroids for GBS, but also provides a basis on which future trials of these regimens could be launched. One major ongoing interest is in pursuing trials of complement inhibitors such as eculizumab because of strong experimental evidence of complement-fixing antibodies to gangliosides in the acute motor axonal neuropathy form of GBS (Willison 2016). An open trial of a C1q inhibitor that will be administered in conjunction with standard IVIg treatment is in progress (NCT04035135). But other approaches besides complement inhibition are also being considered. A multi-centre, open trial of imlifidase, an enzyme that rapidly breaks down IgG, is in progress. The trial plans to recruit up to 30 participants with severe acute GBS and treat them with imlifidase on day 1 and standard IVIg on days 3 to 7. Disease course and outcome will subsequently be compared with matched controls from the International GBS Outcome Study (IGOS; NCT03943589; Jacobs 2017). Furthermore, an open, dose-ranging trial to assess safety and applicability of cord-blood-derived T-regulatory cell product is also being planned (NCT03773328).

Need for better outcome measures

Future trials will need to use the standard GBS disability grade scale to facilitate comparison with previous trials. At the last update of this review we stipulated that we would incorporate the new I-RODS scale in this update (Draak 2014), and we have included it as a secondary outcome. We also recommended the use of minimum clinically important differences (MCIDs) in the selected outcome measures (Merkies 2010). Although almost all the RCTs of GBS that have been conducted used the GBS disability scale, its MCID has never been calculated. One trial that compared plasma exchange with IVIg used less than half a grade difference as the

arbitrary definition of equivalence (Plasma 1997). The MCID in I-RODS has been developed but not validated. We therefore accepted the arbitrary threshold of 6 points on the centile conversion of I-RODS used by the authors of ICA-GBS 2017 and JET-GBS 2018 in our calculations for this review. This decision will need revision in future versions of this review if ongoing work to define the MCIDs of I-RODS prefers a different calculation for this outcome. With more experience, a MCID in I-RODS may become preferred as the primary outcome for this and other reviews of GBS treatments, but a decision about such a change must await the next update.

Potential biases in the review process

This review might be biased by the fact that one of the review authors, RACH, co-authored two of the six included RCTs with two other review authors; one with JP and one with RDMH. We took steps to address this: two review authors who were independent of these trials also extracted and checked data, and independently assessed risk of bias. Two of the review authors (RACH, RDMH) have received funding from companies that manufacture medications that are used or might be used for treating GBS (see [Declarations of interest](#)). RB is Managing Editor of Cochrane Neuromuscular. The editorial process of the review update from peer review to publication was conducted independently.

Not all prespecified outcomes selected for this review were provided by the included trials. Zhang 2000 only reported disability at eight weeks, and neither eculizumab trial reported death or disability at 12 months (ICA-GBS 2017; JET-GBS 2018). In the absence of data at these prespecified time points, we decided to report data at the nearest available time points. All six RCTs were too small to detect rare serious adverse events.

Agreements and disagreements with other studies or reviews

Observational studies of included interventions

There are no observational studies of IFN β -1a in GBS apart from two single case reports of improvement following its use combined with other treatments (Créange 1998; Schaller 2001): such improvement could merely reflect the natural history of the disease. The evidence in this review is insufficient to either support or discourage further investigation of IFN β -1a for GBS.

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. Pursuit of this line of research would require investigation of the optimal combination, route and dose of trophic factors.

Before the trial of CSF filtration was performed, a series of 24 people with acute GBS had received this treatment: 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 Wollinsky 2001 trial, CSF lymphocytic pleocytosis was noted in all 14 people in whom this was assessed. 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 treated with CSF filtration and the procedure has been discontinued in the department responsible for this trial (Ludolph 2010 [pers comm]). The treatment is not known to have been pursued since then and concern about causing meningitis discourages further pursuit of this treatment.

There are no other reports of the use of tripterygium polyglycoside in GBS, and its active ingredients and mechanisms of action are unknown. In the Zhang 2000 trial, tripterygium polyglycoside lowered the inflammatory cytokine interleukin-6 concentration in the serum more than corticosteroids. If it were desired to pursue this treatment it would be necessary to identify the active ingredient or ingredients in the herbal extract.

There is a single report of recovery following the use of eculizumab in a child with GBS, although the diagnostic criteria were not specified (Ram 2014). There have not been any other trials, case series or reports of the use of complement inhibitors in GBS. Because of strong experimental evidence that complement fixing antibodies are important in some types of GBS, there is continued interest in pursuing their use in treatment (Goodfellow 2016).

Treatments tested in other studies

Table 2 summarises these studies.

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 participants receiving allogeneic renal, cardiac or hepatic transplants” (Roche). It is often used in autoimmune diseases but the evidence for its efficacy is limited (Sanders 2008; Burns 2015; Doukaki 2015; Tunncliffe 2018).

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 also treated with IVIg 0.4 g/kg/day and intravenous methylprednisolone 500 mg/day for five consecutive days. There were no meaningful differences 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. There were no meaningful differences 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, sensory impairment and death. 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 for GBS.

Selective digestive tract decontamination

Selective digestive tract decontamination (SDD) has been tested in a retrospective trial 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 2). 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 2). 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 2). None of these studies was large enough to confirm or refute clinically significant benefit or harm of any of these interventions. Although the criteria for the diagnosis were not reported in a form that we could verify, we have also included in Table 2 a series of 27 children treated with hyperbaric oxygen and acupuncture for 10 days and compared with 27 children not so treated (Ding 2015). The trial authors concluded that recovery was faster and more complete in the treated children than the comparison group: in the absence of randomisation in the trial authors' description of treatment allocation it would be unsafe to draw conclusions about the efficacy of these combined treatments.

An extensive electronic search in 2016 did not reveal any other trials than those included in this review (Motamed-Gorji 2017). 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 certainty of the evidence from randomised controlled trials (RCTs) was low or very low. Five trials of pharmacological agents other than intravenous immunoglobulin, plasma exchange or corticosteroids did not show a clinically important effect in people with Guillain-Barré syndrome (GBS), one testing interferon beta-1a against placebo, one brain-derived neurotrophic factor against placebo, one cerebrospinal fluid filtration against plasma exchange, and two testing eculizumab against placebo. None were large enough to show or refute clinically important benefit or harm. A sixth trial suggested that the Chinese herbal medicine tripterygium polyglycoside might be superior to corticosteroids in hastening recovery but this requires confirmation. 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. In addition, further work is needed to identify the

best disability outcome measure in GBS and define its minimum clinically important change.

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 trial 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 and Dr Richard Kay, Hong Kong, for translating [Ding 2015](#). We thank Timothy Benstead and Caroline Morrice for peer reviewing the 2019 update of this review.

The Cochrane Neuromuscular Disease Group Trials Search Co-ordinator, 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 Cochrane Neuromuscular. 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. Cochrane Neuromuscular 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 18-75 years with GBS fulfilling Asbury 1990 criteria within 14 days from the onset of symptoms and having Hughes 1978 disability grade > 3
Interventions	Daily SC 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	<p>Primary: to investigate safety and tolerability of r-metHuBDNF</p> <p>Secondary: to conduct a pilot investigation of the effects of treatment on overall disability after 24 and 48 weeks</p> <p>Assessments were performed on the day of randomisation, and after 2, 4, 8, 12, 24 and 48 weeks, and included performing/determining:</p> <ul style="list-style-type: none"> • general medical examination • disability grade • arm grade • MRC sum score • time taken to walk 10 m • grip strength

Bensa 2000 (Continued)

- vital capacity
- haematology, clinical chemistry and urine analysis

Funding source	Amgen funded the trial and provided the drug and placebo
Declarations of interest	Not given in the paper but the trial authors 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 neuron disease Dates: not given Location: UK and Canada

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation was performed from a computer-generated table of random numbers known only to the trial statistician and hospital pharmacy.
Allocation concealment (selection bias)	Low risk	Quote: "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" Quote: "The patients were randomised by opening an opaque sealed envelope that contained the code number of treatment to be received."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "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 of outcome assessment (detection bias) All outcomes	Low risk	Quote: "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"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants and outcomes are reported. 2 participants died: 1 in the BDNF group 34 weeks after randomisation and 1 in the placebo group before week 2 of the trial
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	High risk	BDNF participants had more severe disease and were randomised later.

ICA-GBS 2017

Methods	Parallel-group, single-centre (in 4 local hospitals), RCT with 2:1 active:placebo allocation
Participants	8 participants with GBS fulfilling the Asbury 1990 diagnostic criteria and having a GBS disability score of at least 3 and within 2 weeks from onset of symptoms

ICA-GBS 2017 (Continued)

Inclusion criteria

- Written informed consent, or witnessed verbal informed consent
- Male or female ≥ 18 years of age
- Participants diagnosed with GBS according to NINDS diagnostic criteria
- Onset of weakness due to GBS within 2 weeks of enrolment
- Participants who are being considered for or already on IVIg treatment
- Unable to walk 10 m independently (grade ≥ 3 on GBS disability scale)
- 1st dose of eculizumab must be started within 2 weeks from onset of weakness and any time during the IVIg treatment period.

Exclusion criteria

- Pregnant, lactating women or participants who wish to become pregnant during the trial period and for 5 months following treatment completion
- Participants who are being considered for or already on plasma exchange
- Clear clinical evidence of a polyneuropathy caused by, e.g. diabetes mellitus (except mild sensory), alcoholism, severe vitamin deficiency, and porphyria
- Immunosuppressive treatment during the last month.
- Severe concurrent disease, inability to comply with trial-related procedures or appointments during 6 months
- Any condition that in the opinion of the investigator could increase the participant's risk by taking part in the trial or confound the outcome of the trial
- Enrolment in another controlled trial of an investigational medical product 6 months prior to consent
- Contraindications to the administration of eculizumab:
 - unresolved *N. meningitidis* infection or history of meningococcal infection
 - unsuitable for antibiotic prophylaxis, known hypersensitivity to eculizumab, murine proteins or any of the excipients
 - known or suspected hereditary complement deficiencies.
 - women of child-bearing potential who are unwilling to use effective contraception during the eculizumab treatment period and for a minimum of 5 months thereafter.

Interventions	Eculizumab 900 mg IV weekly for 4 weeks (4 doses) or placebo identical in appearance and consistency in identical packaging. All participants received IVIg 0.4 g/kg for 5 days and ciprofloxacin 400 mg oral or 500 mg IV for 10 weeks.
Outcomes	<p>Primary safety outcome: Incidence of adverse events and serious adverse events during the treatment period.</p> <p>Primary efficacy outcome: Improvement by one or more grades in the GBS disability score at 4 weeks.</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Ability to walk unaided (GBS disability score ≤ 2) at 8 weeks • Time taken to improve in one grade on the GBS disability score • Time taken to walk independently • Difference in GBS disability score at maximum disability compared with 6 months • Percentage of participants with a clinically relevant improvement in I-RODS score defined as an increase from baseline in I-RODS score by at least 6 points on the centile metric score at 4 weeks and 6 months • Percentage of participants with a clinically relevant improvement in ONLS defined as a decrease from baseline in ONLS score by at least one point at 4 weeks and 6 months • Requirement for ventilatory support (GBS disability score ≥ 5) • Duration of ventilatory support • Recurrence of relapse • Death within first 6 months

ICA-GBS 2017 (Continued)

Baseline defined as week 0, or day 1 prior to drug administration.

Funding source	The trial was investigator-led, funded by Alexion Pharmaceuticals, New Haven, CT, USA and co-sponsored by University of Glasgow and NHS Greater Glasgow
Declarations of interest	The senior trial author has undertaken experimental work demonstrating the efficacy of eculizumab in an animal model of one form of GBS
Notes	The trial authors provided additional information to that in the paper Location: UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation and concealed allocation were performed by computer and an interactive web response system." Quote: "Based on baseline characteristics (mean values for Eculizumab and placebo groups) participants seem to be equally distributed across groups."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation and concealed allocation were performed by computer and an interactive web response system." Manuscript page 5, Study design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "ICA-GBS was designed as a phase 2, single centre 2 : 1 randomised, double-blind , placebo-controlled trial" Manuscript page 5, Study design Quote: "The placebo was an exact match in compound to Eculizumab, without the active ingredient. It was identical in appearance and consistency to eculizumab, and came in identical packaging." Contact with 1st trial author
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The placebo was an exact match in compound to eculizumab, without the active ingredient. It was identical in appearance and consistency to eculizumab, and came in identical packaging."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All predefined outcomes except for 'recurrence of relapse' and 'duration of ventilation' were described in the manuscript text, and further illustrated in the tables and figures. The missing outcomes were provided by the 1st author.
Selective reporting (reporting bias)	Low risk	All predefined outcomes except for 'recurrence of relapse' and 'duration of ventilation' were described in the manuscript text, and further illustrated in the tables and figures. The missing outcomes were provided by the 1st author.
Other bias	Low risk	The trial was funded by the manufacturer of eculizumab but we did not deem this to increase the risk of bias in the absence of any other risk factors

JET-GBS 2018

Methods	Double-blind, parallel group, placebo-controlled, multicentre (13 hospitals in Japan), phase 2 RCT with 2:1 eculizumab to placebo ratio
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JET-GBS 2018 (Continued)

Participants

34 participants with acute GBS (within 2 weeks from onset of weakness), aged ≥ 18 years, fulfilling the [Asbury 1990](#) diagnostic criteria, and having a GBS disability score of 3 (when also progressively deteriorating), 4 or 5

Inclusion criteria

- People ≥ 18 years of age at the time of informed consent
- People with onset of weakness due to GBS < 2 weeks before the time of consent
- People unable to walk unaided for ≥ 5 meters (progressively deteriorating FG3 or FG 4-5)
- People who are undergoing or are deemed eligible for and will start IVIg treatment (generally 400 mg/kg for 5 days)
- People with GBS who can start their 1st dose of eculizumab within 2 weeks from onset of weakness and before the end of the IVIg treatment period
- Women of child bearing potential with a negative result in their pregnancy test. All participants must be able to practice an effective, reliable, medically approved method of contraception during the IP administration period and up to 5 months after IP administration is ended.
- People who can be hospitalised during the IP administration period.
- People who have signed the informed consent form

Exclusion criteria:

- People who are being considered for or already on plasmapheresis
- Pregnant or lactating women
- People showing clear clinical evidence of peripheral polyneuropathy other than GBS, e.g. diabetic (except for mild sensory disturbance) or severe vitamin B1 deficiency related (except for mild sensory disturbance)
- People who have received immunosuppressive treatment (e.g. azathioprine, cyclosporine, tacrolimus, or > 20 mg prednisolone daily) during the 4 weeks prior to providing consent
- People who are known to have severe concurrent disease (such as malignancy with uncontrolled primary tumours or metastatic lesions, severe cardiovascular disease, COPD, or TB)
- People who are unable to comply with trial procedures and the treatment regimen
- People who have received rituximab within 24 weeks prior to providing consent
- People with unresolved *Neisseria meningitidis* infection or a history of meningococcal infection
- People with active infectious diseases determined by the investigator or subinvestigator to be clinically severe, and are not being appropriately treated with antibiotics
- People who cannot be treated with antibiotic prophylaxis due to allergies
- People who are allergic to eculizumab
- People who are known to have or suspected of having hereditary complement deficiencies
- People who have been administered another investigational product within 12 weeks prior to providing consent or are currently participating in another trial
- People with any condition that, in the opinion of the investigator or subinvestigator, could increase the person's risk by participating in trial or could confound the outcome by participating in trial or could confound the outcome of the trial
- People with a history of eculizumab treatment for GBS

Interventions

Weekly IV administration of eculizumab 900 mg ($n = 23$) or placebo ($n = 11$), for the 1st 4 weeks

Outcomes

Primary efficacy outcome: proportion of people who reached GBS disability grade 2 (able to walk 5 m unaided) or lower by week 4.

Primary safety outcome: incidence and severity of adverse events during the trial

Secondary outcomes:

- proportion of people improving by ≥ 1 disability grade from baseline at each visit
- proportion of people with disability $\leq$ grade 2 at each visit
- time to improvement by at least 1 disability grade

JET-GBS 2018 (Continued)

- proportion of people with disability grade 1 (able to run) or 0 (healthy) at week 24
- changes from peak disability grade and disability grade at each visit up to 24 weeks
- proportion of people with a clinically relevant improvement in I-RODS score (≥ 6 centile points increase) and the ONLS score (≥ 1 point decrease) at each visit
- proportion of people requiring ventilator support and its duration
- incidence of relapse
- overall survival
- changes in grip strength (using the Smedley-spring type hand dynamometer)
- manual muscle testing score (sum of scores from 13 muscles, total score 65)
- median and ulnar nerve conduction trial parameters
- vital capacity at each visit from baseline
- proportion of IVIg re-administration

Exploratory outcomes:

- antiganglioside IgG antibodies (GM1, GD1a, GalNAc-GD1a, GQ1b, and GM1/GD1a, GM1/GalNAc-GD1a, GM1/GQ1b, and GD1a/GQ1b)
- eculizumab serum concentrations
- serum haemolytic activity

Funding source	The trial was funded by the Ministry of Health, Labor and Welfare research grants and the Japan Agency for Medical Research and Development. Alexion Pharmaceuticals provided eculizumab and placebo free of charge.
Declarations of interest	Alexion Pharmaceuticals funded the trial drug and one of the trial authors reported personal fees (outside the submitted work) from Alexion Pharmaceuticals.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done centrally by an independent company (ADJUST, Sapporo, Japan) through a computer-generated process and web response system with dynamic allocation and minimisation for functional grade (3 vs. 4 or 5) and age (<60 years vs. ≥ 60 years)".
Allocation concealment (selection bias)	Low risk	Quote: "The study drugs were assigned and labelled with random numbers according to the randomisation table created by ADJUST personnel who were not involved in the conduct or analysis of the trial. Patients, investigators, and study staff were not able to access the randomisation table and were masked to treatment group assignment".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients, investigators, and study staff were not able to access the randomisation table and were masked to treatment group assignment. The ADJUST personnel verified that placebo and eculizumab were indistinguishable in external appearance".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Patients, investigators, and study staff were not able to access the randomisation table and were masked to treatment group assignment. The ADJUST personnel verified that placebo and eculizumab were indistinguishable in external appearance".

JET-GBS 2018 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Outcome data were incomplete for 1 participant in the eculizumab group and 3 participants in the placebo group.</p> <p>Quote: "One patient in placebo group did not receive study drug, because of neurological improvement before administration.</p> <p>One participant in the eculizumab group withdrew consent and discontinued during treatment.</p> <p>Two participants in the placebo group dropped out in the post-treatment period: one with neurological deterioration, and one with depression resulting from severe disability."</p>
Selective reporting (reporting bias)	Low risk	<p>Most outcomes were reported in full. A few prespecified outcomes were not reported in either the main text or supplementary material, including</p> <ul style="list-style-type: none"> change in I-RODS score from baseline: week 1, 2, 3; change in nerve conduction measures from baseline: week 1, 2, 3, 8, 12, 16; change in vital capacity from baseline: week 1, 2, 3, 8, 12, 16. <p>We did not consider that these omissions biased the reporting of the trial since reporting was otherwise exhaustive.</p>
Other bias	Low risk	<p>Alexion provided the trial drug but not other support and we did not consider this a source of bias</p>

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 SC injection 3 times a week starting with 22 µg per injection for the 1st 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	<p>Primary aim: to assess the safety and tolerability of IFNb in GBS</p> <p>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")</p> <p>Secondary aim: to conduct pilot investigations of the effect of IFNb on overall disability in GBS.</p> <p>Outcome measures:</p> <ul style="list-style-type: none"> improvement in disability grade 4 weeks after randomisation improvement by 1 or more disability grade 4 weeks after randomisation improvement in disability grade 24 weeks after randomisation improvement by 1 or more disability grade 24 weeks after randomisation time from randomisation to recovery of unaided walking increase in MRC sum score at week 4 and 24 increase in grip strength at week 4 and 24
Funding source	Serono International provided financial support and supplied the drug and placebo

Pritchard 2003 (Continued)

Declarations of interest The trial authors declared receipt of honoraria or travel grants and departmental research grants from Serono International

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each centre was given trial drug in a computer-generated (information from the authors) random sequence by the trial statistician balanced to achieve a 2:1 ratio of IFNb-1a to placebo
Allocation concealment (selection bias)	Low risk	Each centre was given trial 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 of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were unaware whether the participants received IFNb-1a or placebo
Blinding of outcome assessment (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	One participant died in the IFNb-1a group before week 8 after randomisation. 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 30-50 mL removed, filtered and re-infused usually 5-6 times daily for 5-15 consecutive days (n = 17) versus plasma exchange total 200-250 mL/kg in 5 or 6 treatments daily or on alternate days for 7-14 days (n = 20)
Outcomes	Improvement in GBS disability grade after 28 days Improvement by 1 GBS disability grade after 28 days Improvement in GBS disability grade after 56 days Reaching grade 2 by 56 days Reaching grade 2 by 6 months (having reached grade 2) Relapse

Wollinsky 2001 (Continued)

Side effects

Funding source	Pall Medical (Dreieich, Germany) supplied filters and bidirectional pumps, and trial authors acknowledged financial support from L and B Brandt
Declarations of interest	Not stated
Notes	Location: Germany (2 hospitals)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "by means of Documenta Geigy table"
Allocation concealment (selection bias)	High risk	Quote: "Blocks of two. Investigators aware of block size"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The nature of the interventions means that blinding of participants and personnel was not possible.
Blinding of outcome assessment (detection bias) All outcomes	High risk	High risk of bias for all outcomes except death. No mention of blinding assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	The scores of 2 participants, 1 from each group, who died were carried forward (for calculation of the primary and secondary outcome variables) with the last score before death and the actual score was not given
Selective reporting (reporting bias)	Low risk	Complete case analysis of all outcomes reported
Other bias	High risk	2 participants who underwent plasma exchange had transverse myelitis and were retained in the analysis without presentation of the results without them 1 participant in each group was crossed over: it was not possible to place a spinal catheter in the CSF filtration participant. The plasma exchange participant went into hypovolaemic shock during the first plasma exchange. In both cases the last value under the initial treatment was carried forward for calculation of the primary outcome variable but the actual value was not given. For the calculation of secondary outcome variables these participants were entered as missing values.

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) 60-80 mg daily for 4 weeks and then 30-45 mg daily for 4 further weeks (n = 22), versus IV dexamethasone 15-20 mg daily for 15 days, then 5-10 mg daily for 7 days, then oral prednisone 30-60 mg daily decreased by 5-10 mg daily every 2 weeks (n = 21)

Zhang 2000 (Continued)

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 Location: China

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "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 of participants and personnel (performance bias) All outcomes	High risk	Oral tripterygium polyglycoside compared with IV corticosteroids - no blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigators likely to have been aware of treatment allocation
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; **GBS:** Guillain-Barré syndrome; **IFNβ-1a:** interferon beta-1a; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **IV:** intravenous; **IVIg:** intravenous immunoglobulin; **metHuBDNF:** recombinant methionyl human brain-derived neurotrophic factor; **MRC:** Medical Research Council; **NHS:** National Health Service; **NINDS:** National Institute of Neurological Disorders and Stroke; **ONLS:** Overall Neuropathy Limitations Scale; **RCT:** randomised controlled trial; **SC:** subcutaneous

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. 1 person with CIDP treated with 6-mercaptopurine

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

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Study	Reason for exclusion
Créange 1998	Not a RCT. Single case report of improvement following IFN β -1a. See text and Table 2
De Grandis 1995	Only 8 of 426 participants had GBS and their results were not described separately
Ding 2015	Not a RCT. Although the abstract states that the trial was randomised, the main text does not describe randomisation. "54 cases of GBS admitted to this hospital from March 2009 to October 2013 are selected. They are divided in those according to their treatment. Both groups received standard medical care, including treatment of infections, clearance of airway, maintenance of respiratory function, infusion of gamma globulin, corticosteroids, and B vitamins. The treated group had in addition hyperbaric oxygen and acupuncture." There were 27 in each group.
Feasby 1991	Not a RCT. 3 cases treated with muromonab-CD3. See text and Table 2
Francesconi 1972	No GBS cases included
Gamstorp 1996	Not in GBS. Single case of CIDP treated with 6-mercaptopurine
Garssen 2007	Non-randomised trial 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 double-blind, placebo-controlled trial of IV 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	UV irradiation. It is debatable whether this is a pharmacological treatment but in any case we could not include it because there was no description of randomisation or of time from onset when the UV irradiation was applied
Huang X 1998	Time when treatment given not stated. Treatment was UV irradiation. Allocation was said to be randomised but method unclear
Husstedt 1993	No GBS cases included in a trial of <i>Ginkgo biloba</i> extract
Li 1998	Not stated whether it was randomised. UV irradiation. Time from onset differed between irradiation and control groups
Li 2007	A randomised trial of lymphoplasmaapheresis 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 > 1 year after disease onset. Cross-over design RCT of 4-aminopyridine
NCT03773328	Not started and start suspended
Ostronoff 2008	Not RCT. Single case report of improvement following rituximab in 1 person with GBS following haematopoietic stem cell transplantation. Treatment with rituximab started after the acute phase (40 days after onset of neurological signs).
Palmer 1965	Not in GBS. Single case of CIDP treated with 6 mercaptopurine

Study	Reason for exclusion
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 2
Schaller 2001	Not RCT. Single case of GBS treated with IFNb-1a
Sendhilkumar 2013	Excluded because not a pharmacological treatment and not conducted in the acute phase (RCT of pranayama (yoga) and meditation in rehabilitation)
Tzachanis 2014	Not RCT. Single case report of improvement following alemtuzumab in 1 person with GBS that presented 6 months after treatment for chronic lymphocytic leukaemia. The exact time point when alemtuzumab was started is not noted in the paper, but can be estimated based on the other treatments that were provided as after 20 days from onset of neurological signs.
Umapathi 2014	Proposed RCT of azithromycin in GBS associated with diarrhoea. Not yet started or funded as at 1 March 2015 (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 2
Yuill 1970	Not RCT. Single case report of use of azathioprine
Zagar 1995	Review not a RCT

CI: confidence interval; **CIDP:** chronic inflammatory demyelinating polyradiculoneuropathy; **GBS:** Guillain-Barré syndrome; **IFNb-1a:** interferon beta-1a; **IV:** intravenous; **IVIg:** intravenous immunoglobulin; **RCT:** randomised controlled trial; **UV:** ultraviolet

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	19	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.58, 1.38]
2 Improvement by 1 or more grades after 4 weeks	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.42, 2.77]
3 Death	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.07, 32.29]
4 Participants with 1 or more serious adverse events	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.23, 3.72]

Analysis 1.1. 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.

Analysis 1.3. 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.

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	10	Mean Difference (IV, Fixed, 95% CI)	0.75 [-1.14, 2.64]
2 Improvement in disability grade by one or more points after 4 weeks	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.28, 3.54]
3 Death	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.06, 7.85]
4 Death or disability after 12 months	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.17, 10.25]
5 Serious adverse events	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.28, 3.54]

Analysis 2.1. 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.

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

Analysis 2.4. 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.

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	37	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.62, 0.66]
2 Improvement by 1 or more grades after 4 weeks	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.48, 1.84]
3 Death	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.08, 17.42]
4 Serious adverse events	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Adverse events leading to cessation of treatment	1	37	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.08, 17.42]

Analysis 3.1. 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.

Analysis 3.3. 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.

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

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 4.1. 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.

Comparison 5. Eculizumab versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in disability grade after 4 weeks	2	40	Mean Difference (IV, Random, 95% CI)	-0.23 [-1.79, 1.34]
2 Improvement by 1 or more disability grades after 4 weeks	2	40	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.43, 1.69]
3 Improvement by 6 or more points on the I-RODS score after 4 weeks	2	40	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.38, 2.16]
4 Death	2	38	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.08, 26.86]
5 Improvement in disability grade after 6 months	2	38	Mean Difference (IV, Random, 95% CI)	-0.75 [-3.88, 2.37]
6 Improvement by 1 or more grades after 6 months	2	38	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.78, 1.36]
7 Improvement by 6 or more points on the I-RODS score after 6 months	2	37	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.83, 1.17]
8 Death or disability after 6 months	2	38	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.15, 10.11]
9 Participants with adverse events	2	41	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.88, 1.14]
10 Participants with serious adverse events	2	41	Risk Ratio (M-H, Random, 95% CI)	1.90 [0.34, 10.50]

Analysis 5.1. Comparison 5 Eculizumab versus placebo, Outcome 1 Improvement in disability grade after 4 weeks.

Analysis 5.2. Comparison 5 Eculizumab versus placebo, Outcome 2 Improvement by 1 or more disability grades after 4 weeks.

Analysis 5.3. Comparison 5 Eculizumab versus placebo, Outcome 3 Improvement by 6 or more points on the I-RODS score after 4 weeks.

Analysis 5.4. Comparison 5 Eculizumab versus placebo, Outcome 4 Death.

Analysis 5.5. Comparison 5 Eculizumab versus placebo, Outcome 5 Improvement in disability grade after 6 months.

Analysis 5.6. Comparison 5 Eculizumab versus placebo, Outcome 6 Improvement by 1 or more grades after 6 months.

Analysis 5.7. Comparison 5 Eculizumab versus placebo, Outcome 7 Improvement by 6 or more points on the I-RODS score after 6 months.

Analysis 5.8. Comparison 5 Ecuzumab versus placebo, Outcome 8 Death or disability after 6 months.

Analysis 5.9. Comparison 5 Ecuzumab versus placebo, Outcome 9 Participants with adverse events.

Analysis 5.10. Comparison 5 Ecuzumab versus placebo, Outcome 10 Participants with serious adverse events.

ADDITIONAL TABLES

Table 1. Sensitivity analysis eculizumab versus placebo: random-effects versus fixed-effect analysis

Analysis	Outcome	Random-effects	Random-effects heterogeneity	Fixed-effect	Fixed-effect heterogeneity
Analysis 5.1	Improvement in disability grade after 4 weeks	MD -0.23 (95% CI -1.79 to 1.34)	71%	MD -0.04 (95% -0.83 to 0.75)	71%
Analysis 5.2	Improvement by 1 or more disability grades after 4 weeks	RR 0.85 (95% CI 0.43 to 1.69)	36%	RR 0.92 (95% 0.58 to 1.47)	36%
Analysis 5.3	Improvement by 6 or more points on the I-RODS score after 4 weeks	RR 0.91 (95% CI 0.38 to 2.16)	61%	RR 1.07 (95% 0.75 to 1.54)	61%
Analysis 5.4	Death	RR 1.50 (95% CI 0.08 to 26.86)	Not applicable	RR 1.50 (95% 0.08 to 26.86)	Not applicable
Analysis 5.5	Improvement in disability grade after 6 months	MD -0.75 (95% CI -3.88 to 2.37)	87%	MD 0.24 (95% -0.55 to 1.03)	87%
Analysis 5.6	Improvement by 1 or more grades after 6 months	RR 1.03 (95% CI 0.78 to 1.36)	6%	RR 0.99 (95% 0.76 to 1.28)	6%
Analysis 5.7	Improvement by 6 or more points on the I-RODS score after 6 months	RR 0.99 (95% CI 0.83 to 1.17)	0%	RR 0.99 (95% 0.82 to 1.19)	0%
Analysis 5.8	Death or disability after 6 months	RR 1.21 (95% CI 0.15 to 10.11)	23%	RR 1.40 (95% 0.27 to 7.26)	23%
Analysis 5.9	Participants with adverse events	RR 1.00 (95% CI 0.88 to 1.14)	0%	RR 1.00 (95% 0.86 to 1.16)	0%
Analysis 5.10	Participants with serious adverse events	RR 1.90 (95% CI 0.34 to 10.5)	0%	RR 2.13 (95% 0.43 to 10.61)	0%

CI: confidence interval; **I-RODS:** Inflammatory Rasch-built Overall Disability Scale; **RR:** risk ratio

Table 2. Other treatments studied in case reports, case series or other non-randomised study designs

Reference	Regimen	Number treated	Results
Acupuncture and hyperbaric oxygen			
Ding 2015	Quote: "54 cases of GBS admitted to this hospital from March 2009 to October 2013 are selected. They are divided in those according to their treatment. Both groups received	27 children in each group	At the end of treatment participants were classified as "Cured (resolution of respiratory and global paralysis, no other symptom, normal 4-limb power) Good response (significant improvement of respiratory and global paralysis, 4-limb power raised by 2 grades [not defined] without being normal). Some response (fundamental improvement of respiratory and global paral-

Table 2. Other treatments studied in case reports, case series or other non-randomised study designs (Continued)

	standard medical care, including treatment of infections, clearance of airway, maintenance of respiratory function, infusion of gamma globulin, corticosteroids, and B vitamins. The treated group had in addition hyperbaric oxygen and acupuncture."		ysis, 4-limb power raised by 1 grade without being normal) No response (no improvement of respiratory and global paralysis, 4-limb power not elevated)." 26 out of 27 in treated group were cured or had a good response compared with 20 out of 27 in the comparison group.
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 3-4 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
Mycophenolate mofetil			
Garssen 2007	Oral mycophenolate mofetil 1000 mg a day for 6 weeks All participants and historical controls were treated with IVIg 0.4 g/kg/day and IV methylprednisolone 500 mg/day for 5 consecutive days	26 (126 'historical controls')	The mean change in disability grade was not given. The RR of improving 1 disability grade after 4 weeks was 0.91 (95% CI 0.65 to 1.26) less in the mycophenolate mofetil group than in the controls There were no meaningful differences in other outcomes measured (the ability to walk independently after 8 weeks, time to improve 1 disability grade, need for artificial ventilation, MRC sum score, sensory impairment and death)
Murine monoclonal antibody muromonab-CD3 against CD3 antigen on T cells			
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

Table 2. Other treatments studied in case reports, case series or other non-randomised study designs *(Continued)*

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

CI: confidence interval; **CIDP:** chronic inflammatory demyelinating polyradiculoneuropathy; **EBV infection:** Epstein Barr infection; **IV:** intravenous; **IVIg:** intravenous immunoglobulin; **MRC:** Medical Research Council; **RR:** risk ratio

APPENDICES

Appendix 1. Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies (CRS-Web) search strategy

Search date 28 October 2019

#1 MeSH DESCRIPTOR Guillain-Barre Syndrome AND INREGISTER
#2 "Guillain Barre" AND INREGISTER
#3 "acute polyradiculoneuritis" or "acute polyneuritis" AND INREGISTER
#4 MeSH DESCRIPTOR Polyneuropathies AND INREGISTER
#5 MeSH DESCRIPTOR Polyradiculoneuropathy AND INREGISTER
#6 (inflammatory NEAR neuropathy) or (inflammatory NEAR neuropathies) AND INREGISTER
#7 #1 or #2 or #3 or #4 or #5 or #6 AND INREGISTER

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web) search strategy

Search date 28 October 2019

#1 MeSH DESCRIPTOR Guillain-Barre Syndrome AND CENTRAL:TARGET
#2 "Guillain Barre" AND CENTRAL:TARGET
#3 "acute polyradiculoneuritis" or "acute polyneuritis" AND CENTRAL:TARGET
#4 MeSH DESCRIPTOR Polyneuropathies AND CENTRAL:TARGET
#5 MeSH DESCRIPTOR Polyradiculoneuropathy AND CENTRAL:TARGET
#6 (inflammatory NEAR neuropathy) or (inflammatory NEAR neuropathies) AND CENTRAL:TARGET
#7 #1 or #2 or #3 or #4 or #5 or #6 AND CENTRAL:TARGET

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to October 25, 2019>
Search Strategy:

1 randomized controlled trial.pt. (493165)
2 controlled clinical trial.pt. (93394)
3 randomized.ab. (458827)
4 placebo.ab. (202374)
5 clinical trials as topic.sh. (188928)
6 randomly.ab. (320580)
7 trial.ti. (207030)
8 or/1-7 (1247415)
9 exp animals/ not humans.sh. (4637337)
10 8 not 9 (1147399)
11 guillain barre syndrome.tw. or Guillain-Barre Syndrome/ (9423)
12 polyradiculoneuropathy/ or polyneuropathies/ (8669)
13 (acute polyradiculoneuritis or acute polyneuritis).mp. (184)
14 (inflammatory adj5 neuropath\$3).tw. (2913)
15 (inflammatory adj5 polyneuropath\$3).tw. (2112)
16 Acute motor axonal neuropathy.tw. (341)

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

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17 or/11-16 (19308)
18 10 and 17 (641)
19 review.pt. (2572924)
20 18 not 19 (424)
21 remove duplicates from 20 (422)

Appendix 4. Embase (OvidSP) search strategy

Database: Embase <1974 to 2019 October 25>

Search Strategy:

1 crossover-procedure.sh. (61418)
2 double-blind procedure.sh. (167948)
3 single-blind procedure.sh. (37219)
4 randomized controlled trial.sh. (579026)
5 (random\$ or crossover\$ or cross over\$ or placebo\$ or (doubl\$ adj blind\$) or allocat\$).tw,ot. (1709680)
6 trial.ti. (285523)
7 clinical trial/ (964570)
8 or/1-7 (2436655)
9 (animal/ or nonhuman/ or animal experiment/) and human/ (1881937)
10 animal/ or nonanimal/ or animal experiment/ (3874608)
11 10 not 9 (3233732)
12 8 not 11 (2276659)
13 limit 12 to (conference abstracts or embase) (1924645)
14 Guillain Barre Syndrome/dt (2664)
15 Guillain Barre syndrome/dt [Drug Therapy] (2664)
16 Polyneuropathy/dt or Polyradiculoneuropathy/dt (1588)
17 (guillain barre syndrome or acute polyradiculoneuritis or acute polyneuritis or Acute motor axonal neuropathy).tw. (11265)
18 (inflammatory adj5 (neuropath\$3 or polyneuropath\$3)).tw. (7150)
19 or/14-18 (19235)
20 13 and 19 (1371)
21 review/ (2412516)
22 (ivig or plasma exchange).ti. (6060)
23 21 or 22 (2418249)
24 20 not 23 (828)
25 remove duplicates from 24 (817)

Appendix 5. ClinicalTrials.gov search strategy

Search date 17 October 2019

ClinicalTrials.gov - Advanced search

Condition or disease: Guillain-Barre syndrome

Study type: Interventional studies (clinical trials)

Intervention/treatment: ALL

Appendix 6. WHO (ICTRP) platform search strategy

ICTRP - Advanced search

Condition: Guillain-Barre syndrome

Intervention:

Recruitment status: ALL

WHAT'S NEW

Date	Event	Description
28 October 2019	New search has been performed	Search updated. 2 RCTs of eculizumab included

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

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Date	Event	Description
		We incorporated the new I-RODS scale.
14 January 2019	New citation required and conclusions have changed	New first author. We included two new trials of eculizumab. The certainty of evidence was too low to determine benefit or harm.

HISTORY

Protocol first published: Issue 8, 2010

Review first published: Issue 3, 2011

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.
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 Discussion as a potential intervention.

CONTRIBUTIONS OF AUTHORS

AD wrote the first draft of this update. All authors checked and edited subsequent drafts and approved the final version.

AD became the first author of this update. RB, the Managing Editor of Cochrane Neuromuscular became an author at the 2016 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

AD declares that her host institution, the Erasmus MC, pays her salary with a fund from Annexon Biosciences (January 2017), a pharmaceutical company that develops complement inhibitors for GBS. Neither her PhD research nor her employment is contingent on this funding, and AD has no control over the use of the funds. AD has also received an honorarium for a lecture from CSL Behring (November 2018). The money was paid directly to the Erasmus MC and AD did not financially benefit from this honorarium.

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 former department received financial support for two trials included in this review, from Amgen for the [Bensa 2000](#) trial and from Serono for the [Pritchard 2003](#) trial. Neither showed a significant beneficial effect of the drug tested. RACH holds consultancies with LFB, which manufactures human immune globulin used in the treatment of Guillain-Barré syndrome (GBS) but specifically excluded from this review. RACH was co-chair of the steering committee of a negative trial of fingolimod in chronic inflammatory demyelinating polyneuropathy (CIDP), a condition related to GBS, conducted by Novartis. RACH serves as honorary Board member of the GBS CIDP Foundation International and medical patron of GAIN (Guillain-Barré & Associated Neuropathies), charity, which serves the interests of people with GBS.

Dr Hadden has nothing to declare relating to the current review, but declares financial relationships with Grifols (advisory board membership, development/chair/publication of educational presentations, conference travel expenses, project grant to department to pay nurse salary); CSL Behring (advisory board membership, conference travel expenses, lecturing and co-authorship of published review,

and project grant to department to pay nurse salary); and KIMS Hospital (shareholder). He is a co-author of one of the trials 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 intravenous immunoglobulin (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 the 2016 update. AD joined and became the first author of the review for this update.

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

We made the following changes to the methods in accordance with MECIR standards ([Higgins 2018](#)) and the Cochrane Neuromuscular standard protocol:

- added a section on '[Unit of analysis issues](#)' to describe methods for inclusion of multiple-arm trials, should they be available in future updates;
- included rule-of-thumb thresholds for interpretation of the I^2 statistic;
- specified that we would use a random-effects model for meta-analysis;
- described GRADE assessment in more detail;
- removed assessment of 'explicit diagnostic criteria' from the 'Risk of bias' methods;
- specified use of random-effects analysis with a sensitivity analysis comparing random-effects and fixed-effect analysis, in any future meta-analysis

We also cited a minimum clinically important difference of change in average Guillain-Barré syndrome disability grade in the methods.

At the last update of this review we stipulated that we would incorporate the new Inflammatory Rasch-built Overall Disability Scale (I-RODS) in this update ([Draak 2014](#)). We included it as a secondary outcome and in the 'Summary of findings' table.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cerebrospinal Fluid; Brain-Derived Neurotrophic Factor [*therapeutic use]; Guillain-Barre Syndrome [*therapy]; Interferon beta-1a [*therapeutic use]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Adult; Female; Humans; Male; Middle Aged