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Clinical and economic outcomes of therapeutic plasma exchange and intravenous immunoglobulin for treating adults with autoimmune neurological disorders: a systematic review and meta-analysis

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Abstract

Background Therapeutic plasma exchange (TPE) and intravenous immunoglobulin (IVIG) are high-cost treatments used for relapsed or refractory autoimmune neurological disorders.

Objective To compare the effectiveness, safety and economic outcomes of therapeutic plasma exchange (TPE) compared with intravenous immunoglobulin (IVIG) for treating autoimmune neurological disorders.

Methods MEDLINE, Embase, PubMed, The Cochrane Library, Transfusion Evidence Library, ClinicalTrials.gov and WHO ICTRP were searched from inception to 30th April 2025. Only randomised controlled trials (RCTs) involving people diagnosed with any autoimmune neurological disorders and comparing TPE with IVIG were included. Quality of the included studies was assessed via Cochrane risk of bias tool (ROB2). Meta-analysis was performed when feasible. Additionally, a rapid review was conducted on model-based economic evaluations for treating MG, GBS, and CIDP to identify and highlight existing gaps and limitations in included clinical trials for developing an economic model. A review protocol was pre-registered at PROSPERO 2024 CRD42024552257.

Results Fifteen RCTs were eligible for inclusion: five for myasthenia gravis (MG) ($N=247$), eight for Guillain-Barré Syndrome (GBS) ($N=887$) and two for chronic immune-mediated polyradiculoneuropathy (CIDP) ($N=32$). No trials were found for any other disorders. The trials were at low to high risk of bias. For MG there was no difference between TPE and IVIG at three weeks on the functional improvement scale (SMD 0.31, 95% confidence interval – 0.01 to 0.64,

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low-certainty evidence). No significant differences were found with regard to the frequency of serious adverse events (SAEs), any adverse events (AEs), length of hospital stay or quality of life on the MG-QoL60 and MG-QoL15 scales. The mean overall direct medical cost was approximately 1.4 times higher in the IVIG group compared to the TPE group. For GBS, there was no significant difference at three to six weeks on functional improvement scale (SMD = -0.65 95% CI -1.40 to 0.11, low-certainty evidence). Two studies comparing mean and median direct cost between IVIG and TPE for GBS patients showed that IVIG group impose approximately 1.5 times higher costs than TPE. Data on other outcomes were limited and economic evaluation for indirect costs, disutilities due to AEs and carer disutilities were absent.
For CIDP, limited data showed a lower level of deficit at 6 weeks with no significant difference between TPE and IVIG (MD 15.00, 95% CI -16.37, 46.37) and no difference regarding SAEs or any other AEs. No trials estimated costing.

Conclusion The effectiveness and safety of TPE were comparable to IVIG for treating autoimmune neurological disorders, although data are limited. TPE conveys lower overall healthcare costs than IVIG.

Keywords Therapeutic apheresis, Plasma exchange, Intravenous immunoglobulin, Myasthenia gravis, Guillain-Barré syndrome, Chronic immune-mediated polyradiculoneuropathy

Background

Autoimmune neurological disorders are clinically and pathologically diverse. There are 0.8–1.9 cases per 100 000 people per year worldwide of Guillain-Barré Syndrome (GBS) [1] 2.84 per 100 000 of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) compared with 0.42 per 100 000 cases of antimyelin-associated glycoprotein (MAG) neuropathy in England [2]. The prevalence of some of these disorders, such as myasthenia gravis (MG) [3] and CIDP among diabetics [4] are increasing. These disorders affect all age groups.

Current treatments aim to suppress or modulate the underlying dysimmune processes using a range of approaches including therapeutic plasma exchange (TPE, sometimes referred to as PLEX) or intravenous immunoglobulin (IVIG.) [5, 6]. Plasma exchange requires an apheresis machine and apheresis specialists to do the procedures. The procedure is done by exchanging patient plasma for either human albumin solution, or plasma. Intravenous immunoglobulin is derived from blood donors and is given as an intravenous infusion. While this requires trained medical or nursing staff for administration, it does not require the extensive training required for performing plasma exchange. TPE works by eliminating plasma circulating pathogenic substances, including autoantibodies [7] and IVIG competes with autoantibodies, increases the turnover of endogenous IgG, inhibits complement, downregulates cytokines, co-stimulatory and cell adhesion molecules, and enhances the activity of inhibitory Fc-receptors [8]. In TPE, patient plasma is separated from blood using filtration or centrifugation. Donor plasma replaces the patient plasma that has been removed and blood is then returned to the patient. In immunoadsorption and double filtration plasma exchange, the patient undergoes an apheresis procedure where plasma is separated from blood. However, there is then a filtration step to remove proteins such as immunoglobulins and then the patient's own plasma is returned along with their other blood cells [9].

TPE or IVIG have been recommended for treating several autoimmune neurological diseases [10, 11]. Over 12 months from April 2023 to March 2024 in the United Kingdom, IVIG was given to 1650 patients with CIDP (1,381,729 g), 728 with MG (185,879 g) and 838 with GBS (123,289 g) [12]. Overall for these three conditions this was 3216 patients and 1,690,897 g at an approximate cost of £133,580,863 for one year. In addition to the high costs of these interventions, healthcare utilization by patients with these conditions can be intensive with a high proportion requiring intubation, intensive care, and prolonged hospital admissions.

In this review, we compared the effectiveness, safety, and costs of TPE and IVIG, and conducted a rapid review of economic evaluation models to identify gaps and limitations in data reported in included trials for economic modeling within this area.

Method

The PRISMA checklist 2020 [13] was used for developing and reporting on this review. A pre-specified protocol was registered at PROSPERO 2024 CRD42024552257.

Eligibility criteria

Randomised controlled trials (RCTs) conducted in any settings and involving adults who were diagnosed with autoimmune neurological conditions such as myasthenia gravis (MG) and Guillain-Barré syndrome (GBS) were eligible for inclusion (see Appendix A for the full list). RCTs in multiple sclerosis, lupus, neuromyelitis, POEMS syndrome, motor neurone disease, Parkinson's disease and paraproteinemic demyelinating neuropathy (PPN) were excluded.

RCTs testing TPE or any other alternatives (plasmapheresis and plasma filtration adsorption/ immunoadsorption)

versus IVIG of any dose and any frequency were included. Data were extracted for the following review primary outcomes: disease functional scales measured by condition-specific standardised scale at any of the following time points (up to 3 weeks, 3–6 weeks, at 12 weeks); quality of life measured by any standardised scale at any time points; Time to improvement of one level on the disease-specific functional scales; Time to improvement of one level on the quality of life scales; Serious adverse events (SAEs) as defined in the included studies and adverse events (AEs) at any grade. Review secondary outcomes were length of hospital stay, admission to intensive care unit (ICU), intubation, number of clinic visits/clinic time, need for informal care, days lost from work, time to return to work, antibody levels, mortality at 1 year, and any reported cost data.

Patient involvement

A patient representative (EH) reviewed the protocol, commented on our chosen outcomes, read and commented on the final manuscript.

Search strategy and study selection

A comprehensive search strategy was developed and the following databases were searched from inception to 30 April 2025 for systematic reviews and RCTs: MEDLINE, Embase, PubMed, The Cochrane Library, Transfusion Evidence Library, ClinicalTrials.gov and WHO ICTRP. MEDLINE, Embase and Transfusion Evidence Library were also searched from inception to 30 April 2025 for economic evaluations. No restrictions were applied by date, language or setting. The references of eligible studies and relevant reviews were also hand searched to identify any additional studies not retrieved by the electronic search. Search strategies are presented in Appendix B.

Three reviewers (CD, CK, RM) independently screened all the titles and abstracts and full texts against the review eligibility criteria using Covidence [14]. Data extraction and risk of bias (RoB) assessment were undertaken by at least two reviewers (CD, CK, RM). The quality of the included studies was assessed for all outcomes using the Cochrane Risk of Bias 2 (ROB2) tool [15].

Data syntheses

When the same outcome was reported by at least two trials, data were pooled using a random effects model. For continuous data, the mean difference with 95% confidence interval (CI) was used for trials using the same scale. Where different scales were used to measure the same outcome, standardised mean difference (SMD) with 95% CI were used. Odds ratios (OR) were used for pooling dichotomous data. All outcomes were analysed separately by neurological condition. The GRADE method [16] was used to assess all review primary outcomes evidence.

Economic evaluation review methods

Model-based economic evaluation studies focused on the treatment of MG, GBS, and CIDP were identified to define the approaches used for these diseases and recognize the key parameters involved in an economic evaluation. We compared the outcomes used in economic evaluation studies with those reported in the included RCTs to identify and highlight existing gaps in outcome reporting.

All the published economic evaluation models were reviewed for each autoimmune neurological disorder to identify different types of models in this area, determine the key parameters for assessing the cost-effectiveness of interventions, and highlight any existing gaps. Cost data from included studies, and from economic models were converted to 2024 UK pounds (GBP) using CCEMG-EPPI-Centre Cost Converter (version 1.7) [17]. For a full description of methods involved in the economic evaluation, see Appendix C.

Results

Results of the search

2,799 records were identified, 2,115 from database searching, with a further 323 records searching with NICE health economic filters, and 321 records from trial registers. 1,951 records were screened after duplicates were removed. 1,836 irrelevant records were excluded at title and abstract screening. 115 reports were retrieved for full text screening. 66 reports were excluded with reasons of wrong intervention/comparator ($n=29$), wrong study design ($n=35$), retracted study ($n=1$) and wrong population ($n=1$). A list of studies excluded after full text screening is available in Supplementary Table S1. Fifteen RCTs were eligible for inclusion [18–32], published in 44 records (See appendix D), three were ongoing studies [33–35], and two [36, 37] were records awaiting classification, both trial registrations of unknown status with no associated publication. Five trials were on MG, eight were on GBS and two on (CIDP) (Fig. 1).

Therapeutic plasma exchange (TPE) versus intravenous immunoglobulin (IVIG) for Myasthenia Gravis (MG)

Description of included studies

Five trials were included, one from each of the following countries: Iran [18], Canada [19], France [24], China [27], and Denmark [29]. Three trials included adults with moderate to severe generalised MG [18, 19, 29]. No information on MG severity was reported in two trials [24, 27]. All trials compared one type of TPE to IVIG except one27 where double-filtration plasmapheresis (DFPP) and immunoadsorption (IA) were compared to IVIG. Three trials [19, 24, 27] measured the changes in functional scales outcome at three weeks and one [19], at three to six weeks. Myasthenia Gravis Score for disease severity (QMGS) was used in one trial [19],

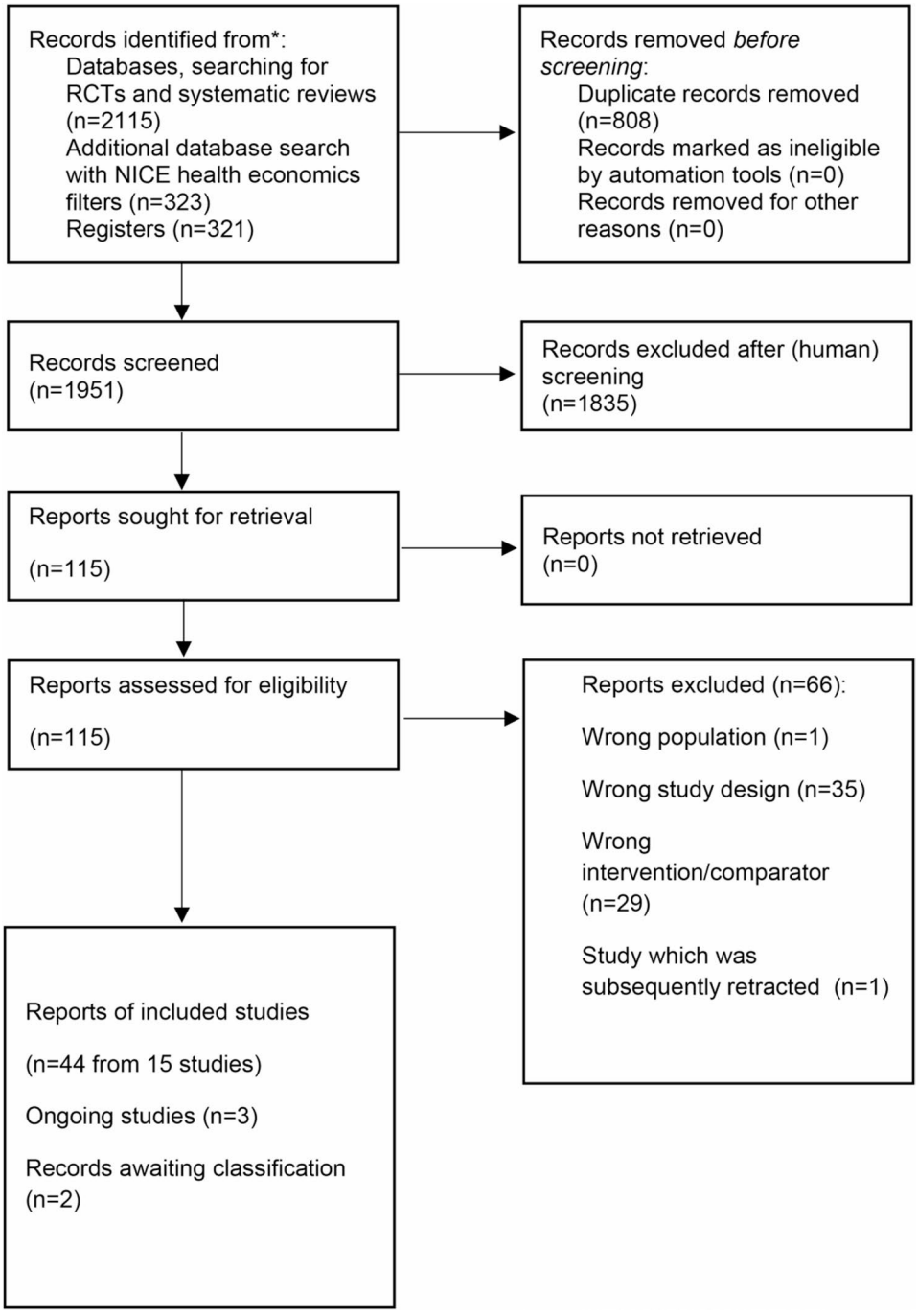

Fig. 1 PRISMA flow diagram

myasthenic muscular score (MMS) in one trial [24], and Quantitative Myasthenia Gravis (QMG) score in one trial [27]. Two trials [24, 27] reported on time to improvement of one point on functional scales. AEs at any grade were reported in two trials [24, 29] and SAEs in one trial [19]. Only one trial [19] measured health-related quality of life (HRQoL) at up to 3 weeks and at three to six weeks using MG-QoL60 and MG-QoL15 scales). Details of characteristics of included studies are in Table 1. A summary of outcomes reported per trial is in Supplementary Table S2.

Risk of bias

One trial [19] was at high RoB due to missing data. The other four trials [18, 24, 27, 29] had some concerns, most commonly due to lack of published trial registration (4/5 trials) [18, 24, 27, 29] or due to no description of randomisation and allocation concealment (3/5) [18, 19, 27], (See Fig. 2).

Table 1 Characteristics of included studies

Study ID trial design, recruitment period,	Inclusion criteria	Exclusion criteria	Age, Participant characteristics: *N*, age, disease severity	Details of TPE: interventions	Details of IVIG interventions	Study Outcomes
MG						
Athena Alipour-Faz 2017, Iran RCT, parallel group Recruitment period: 2014-15 *N* = 24 (TPE: 12; IVIG: 12)	Adults with confirmed diagnosis of Myasthenia Gravis (MG). Presence of thymoma, with generalized MG with positive acetylcholine receptor antibody, without ocular MG and no contraindication to thymectomy	Exacerbation of MG secondary to current medications; infection; Irregular medical treatment; Change in the dosage of the immunosuppressant; History of anaphylaxis to IVIG and albumin; Clinically significant cardiovascular disease; Bleeding disorders	**Age**: TPE: 35.00 ± 11.39 years IVIG: 37.00 ± 8.6 years **Female, n (%)**: TPE: 6 (50%) IVIG: 6 (50%) **Height**: NR **Weight**: NR **Disease severity**: Median duration of disease (Median; range) months, TPE:11 (2-144) months; IVIG: 4 (1–11) months	5 × 1 L plasma exchange with 5% albumin replacement fluid every other day, 10–30 days pre-thymectomy	1 g/kg/day of IVIG for 2 consecutive days, 10–30 days pre-thymectomy	**Primary outcome**: Duration of hospitalisation; Length of ICU stay after surgery; Length of intubation period; Duration of surgery; Dose of steroid **Secondary outcomes**: Survival rate; Side effects
Barth 2011, Canada RCT, parallel group Recruitment period: 2007-10 *N* = 84 (TPE: 43; IVIG: 41)	Adults with moderate to severe MG-QMGS > 10.5 and worsening weakness requiring a change in treatment modality, as judged by a neuromuscular expert	MG worsening secondary to concurrent medications (e.g., aminoglycosides) or infection; Change in corticosteroid dosage in the 2 weeks prior to screening; Other disorders causing weakness, Known immunoglobulin A deficiency; Active renal or hepatic disease; Clinically significant cardiac disease; Known hyperviscosity or hypercoagulable state; History of anaphylaxis, severe systemic response to IVIg or albumin; Known refractory status to previous IVIg or PLEX; Poorly controlled hypertension; Pregnancy, or breastfeeding.	**Age**: TPE: 58 ± 17, range 20–84 years; IVIG: 57 ± 18, range 19–84 years **Female, n (%)**: TPE: 24 (55%); IVIG: 24 (58%) **Height**: NR **Weight**: NR **Disease severity**: Baseline QMGS TPE: 14.44 ± 3.8; IVIG: 41 ± 14.26	5 × 1.0 plasma volume exchanges with 5% albumin replacement fluid given every second day, with breaks over the weekend allowed	1 g/kg/day of IVIg (Gamunex ® Talecris Biotherapeutics, Mississauga, Canada) for 2 consecutive days	**Primary outcome**: Change in QMGS from baseline to day 14 after full treatment **Secondary outcomes**: Change in QMGS from baseline to days 21 and 28; Change in Single Fiber Electromyography: jitter, abnormal pairs, blocking pairs; % decrement in RNS (repetitive nerve stimulation) from baseline to days 14, 21, and 28; Postintervention status at days 14, 21, and 28; Change in AChRAb titers from baseline to days 28 and 60; Need for ICU admission, positive pressure ventilation or intubation; Any hospitalization; Additional therapy for MG (permitted after day 14, if necessary); Adverse events occurring within 30 days

Table 1 (continued)

Study ID trial design, recruitment period,	Inclusion criteria	Exclusion criteria	Age, Participant characteristics: *N*, age, disease severity	Details of TPE: interventions	Details of IVIG interventions	Study Outcomes
Gajdos 1997, France RCT, parallel group Recruitment period: 1991–1995 *N* = 87 (TPE: 41; IVIG: 46)	Diagnosis of MGpresenting with myasthenic exacerbation within past month	Known allergy to IVIG or with contraindications to PE (i.e. coagulation disorders, cardiovascular instability, coronary insufficiency, uncontrolled infection or pregnancy)	**Age**: TPE: 50.5 ± 20.5 (Range: 15–91); IVIG: 49.4 ± 16.6 years (Range: 20–83) **Female, n (%)**: TPE: 28 (68%); IVIG: 29 (63%) **Height**: NR **Weight**: NR **Disease severity**: Myasthenic muscular score: TPE: 50.5 ± 15.7; IVIG: 52.6 ± 15.4	3 x TPE of 1.5 volumes given post-day 0 (randomization) on days 1, 3 and 5. One plasma volume (PV) was calculated according to the following formula: PV = (1 - haematocrit) X 70 X body weight (kg) Replacement fluid was composed of equal parts of 4% diluted albumin and artificial gelatin solution. No IVIG infusion after PE was allowed	Daily 0.4 g/kg doses (chromatography-purified and solvent detergent-treated polyvalent Igs, Gammachron, LFB, France) for either 3 (total 1.2 g/kg) or 5 (total 2 g/ kg) consecutive days	**Primary outcome**: Change in myasthenic muscular score (MSS) ranging between 0 and 100 (normal score) between randomization and day 15 **Secondary outcomes**: Time to the occurrence of a treatment response within the first 2 weeks, defined as anincrease in muscular score of at least 20 points compared with the initial value; Relative variation of anti-AChR antibody titers between day 0 and day 15; Adverse events
Liu 2010, China RCT, parallel group Recruitment period: NR *N* = 40 (DFPP: 15; IA: 10; IVIG: 15)	NR	NR	**Age**: DFPP*: 55.2 ± 1.4; IA**: 57.2 ± 2.4; IVIG: 53.2 ± 1.7 **Female, n (%)**: DFPP: 6 (40%); IA: 4 (40%); IVIG: 7 (47%) **Height**: NR **Weight**: NR **Disease severity**: QMG score pre-treatment: DFPP: 19.4 ± 2.2; IA: 16.3 ± 2.0; IVIG: 16.5 ± 1.7	3 TPE treatments (automated double filtration method) every 24–48 h. The exchanged plasma volume ranged from 2500 to 3000 mL depending on the weight of the patients (40 mL/kg)	0.4 g/kg/day IVIG for 5 days	**Primary outcomes**: Changes in autoantibodies 2 weeks after treatment: titin antibodies (Titin-ab); acetylcholine receptor antibodies (AChR-ab); presynaptic membrane antibody (PrsmR-ab). Change in immunoglobulin G and albumin levels **Secondary outcomes**: Relative QMG score - calculated as (Pre-QMG score - Post-QMG score)/Pre-QMG score; Recovery rate (relative score >/=95%); Partial recovery rate (80% to 95% relative score); Notable efficacy rate (from 50% to 80% relative score) Improvement rate (25% to 50% relative score) Clinical remission rate (> 25% relative score) Clinical efficacy rate (> 50% relative score)

Table 1 (continued)

Study ID trial design, recruitment period,	Inclusion criteria	Exclusion criteria	Age, Participant characteristics: *N*, age, disease severity	Details of TPE: interventions	Details of IVIG interventions	Study Outcomes
Rønager 2001, Denmark RCT, crossover Recruitment period: NR *N* = 12 (PE-IVIG: 4; IVIG-PE: 8)	Adults aged 18–75 with generalised MG; Osserman Class 3 to 5; Functional status 4 to 5; Previous receipt of immunosuppressive treatment with either azathioprine or prednisone; Seropositive with a positive antiacetylcholine receptor (AChR) antibody titer: Significant decrement (15%) during repetitive stimulation at the time of diagnosis	Known or suspected allergy to IVIG; Hypogammaglobulinemia, including lack of IgA; HIV antibody positive; Impaired renal function; Pregnancy, lactation or fertile women without use of acceptable contraception; Psychosis; Other major diseases such as active cancer or severe cardiac problems; Disturbances of coagulation, including anticoagulation treatment	**Age: T**PE followed by IVIG (PE-IVIG): mean 46.25 [calculated]; IVIG followed by TPE (IVIG-PE): mean 46.5 [calculated] **Female, n (%)**: PE-IVIG: 4 (100%); IVIG-PE: 5 (63%) **Height**: NR **Weight**: NR **Disease severity**: NR	Five treatments, one given every other day. A Gambro-catheter was placed in the subclavian, internal jugular, or the femoral vein. 5% body weight plasma exchange over 3 h. The plasma passed through a filter, which removed plasma proteins with a diameter less than 0.2 micrometers. The lost plasma was substituted with Ringer's lactate and a 20% solution of albumin	400 mg/kg body weight IVIG as a 5% solution once a day for five days. The preparation was Gammagard S/D from Baxter (Glendale, CA, U.S.A.), a virus inactivated humane immunoglobulin for intravenous use, prepared by alcohol fractionating plasma from healthy adults	**Primary outcome**: Change in QMGS 7 days after treatment **Secondary outcomes**: Decrease in anti-AChR (antiacetylcholine receptor) antibody titre 7 days, 4 weeks, 8 weeks and 16 weeks after treatment; change in decrement at repetitive stimulation at 3 Hz 7 days, 4 weeks, 8 weeks and 16 weeks after treatment; Change in QMGS at 4, 8 and 16 weeks
GBS						
Bril 1996, Canada RCT, parallel group Recruitment period: 1991-93 *N* = 50 (TPE: 24; IVIG: 26)	Adults fulfilling the NINCDS criteria for GBS; Disability grade ≥ 2; Age ≥ 14 years; Ability to provide informed consent.	Purely sensory symptoms; Cranial nerve palsies without significant limb weakness; Previous acute polyneuropathy; Improvement of one or more disability grades before randomization; Pregnancy or other significant potentially etiologic or interfering medical condition; Inability to be followed for 12 months	**Age**: TPE: 49.3 ± 4.0; IVIG: 39.9 ± 3.4 Range (both groups): 17 to 85 years **Female, n (%)**: TPE: 11 (46%); IVIG: 13 (50%) **Height**: NR **Weight**: NR **Disease severity**: Mean disability grade at baseline: TPE: 4.1; IVIG: 3.8	Total plasma volume of 200 to 250 ml/kg exchanged over 5 treatments, distributed over 7–10 days, using continuous flow technique with centrifugal or membrane cell separation	0.5 g/kg/day IVIG on 4 consecutive days, for a total dose of 2.0 g/kg. (IVIG supplied by Canadian Red Cross, obtained from Miles Canada Inc., Cutter Biological (Etobicoke, Ontario))	**Primary outcome**: Time to improve one disability grade **Secondary outcome**: Disability grade at 1 month (DGI); Time to reach DG1 - i.e. a state of minimal symptoms and/or findings;
Chaudhuri 2014, India RCT, parallel group Recruitment period: 2008–2012 *N* = 40 (TPE: 19; IVIG: 21)	Adults with GBS subtypes AIDP, AMAN & AMSAN; Isolated tachycardia; Persistent hypertension Fluctuations in heart rate < 30 beats/min over 24 h; Blood pressure fluctuations < 20/10 mm Hg over 24 h	"Most patients with autonomic disturbances were excluded."	**Age**: TPE: 43.4 ± 13.1; IVIG: 41.6 ± 12.4 **Female, n (%)**: TPE: 7 (39%); IVIG: 7 (37%) **Height**: NR **Weight**: NR **Disease severity**: Mean length of hospital stay at baseline: TPE: 20.5 ± 2.9; IVIG: 15.1 ± 2.2	Removal of total of 200 -250mL/kg of plasma over 5–8 cycles with replacement fluid either 5% albumin (15 pts) or FFP (4 pts), on daily basis. Most patients received 5 cycles.	0.4 g/kg per day for 5 consecutive days	**Primary outcome**: Change in mean motor power, measured by Medical Research Council (MRC) muscle strength score at admission and discharge **Secondary outcomes**: Hughes grade (scale for assessing functional motor deficits) at discharge; Effectiveness and duration of hospital stay; Cost effectiveness of therapy

Table 1 (continued)

Study ID trial design, recruitment period,	Inclusion criteria	Exclusion criteria	Age, Participant characteristics: *N*, age, disease severity	Details of TPE: interventions	Details of IVIG interventions	Study Outcomes
Diener 2001, Germany RCT, parallel group Recruitment period: 1994–1997 *N* = 76 (of planned 279) randomised: (TPE: 26; IA: 25; IVIG: 25) 67 received treatment: (TPE: 26; IA: 18; IVIG: 23)	Adults with acute severe or moderate idiopathic demyelinating polyradiculoneuropathy (Guillain-Barré syndrome), lasting less than 14 days	NR	**Age**: NR **Female, n (%)**: NR **Height**: NR **Weight**: NR **Disease severity**: NR	Five treatments of plasma exchange [No further treatment details given]	0.4 g/kg/day immunoglobulin (Gammonativ®) for 5 consecutive days	**Primary outcome**: Clinical improvement by at least one grade of the functional score at day 28 post-randomisation **Secondary outcomes**: Clinical improvement by at least one grade of the functional score 6 and 12 months after randomisation; Interval between the onset of neurological symptoms and a one grade improvement in the functional score; Duration of endotracheal intubation; Time to reach grade 1 of the functional score; Duration of hospital stay; Duration of stay in rehabilitation
Hughes 1997 International multi-centre trial (38 centres, 11 countries†) Recruitment period: 1993–1995 *N* = 383 (TPE: 123; IVIG: 131; PLEX+IVIG: 129) [4 withdrawn as ineligible]	Age over 16 years; Onset of neuropathic symptoms within the previous 14 days; Confirmed diagnosis by a qualified neurologist; Satisfaction of accepted clinical and cerebrospinal-fluid diagnostic criteria; Severe disease (requiring aid to walk or worse); "	Atypical forms of Guillain-Barré syndrome; Serious pre-existing other disease; Contraindications to PE or IVIG	**Age**: TPE: 51.0 ± 16.5; IVIG: 51.5 ± 17.9 **Female, n (%)**: TPE: 47 (39%); 51 (39%) **Height**: NR **Weight**: NR **Disease severity**: Disability grade at baseline: TPE: 3.9 ± 0.5; IVIG: 4 ± 0.5	5 × 50 mL/kg plasma exchanges to total of 250 mL/kg during 8–13 days post-randomisation. If an exchange was inadequate, a sixth exchange was given to achieve total required.	0.4 g/kg IVIG (Sandoglobulin, Sandoz, Basel, Switzerland) daily for 5 days starting on the day of randomisation (day 1)	**Primary outcome**: Change on 7point-disability grade scale 4 weeks after randomisation. **Secondary outcomes**: Time from randomisation to unaided walking; Time to permanent discontinuation of artificial ventilation; Average rate of recovery derived from the changes in disability grade over the 48-week follow-up period; Number of deaths; Proportion of patients still unable to walk without aid (grade 3) after 48 weeks; Time to hospital discharge; Time to return to work

Table 1 (continued)

Study ID trial design, recruitment period,	Inclusion criteria	Exclusion criteria	Age, Participant characteristics: *N*, age, disease severity	Details of TPE: interventions	Details of IVIG interventions	Study Outcomes
Haridy 2023, Egypt RCT, parallel group Recruitment period: 2021–2022 *N* = 81 TPE: 54; IVIG: 27	Aged 18 to 70 years; Within the first two weeks of disease onset	Metabolic and electrolyte disorders (hypokalaemia or hyperkalaemia); Periodic paralysis; Hypoglycemia; Malignancy; Other causes of peripheral neuropathy; Other causes of acute paralysis of limbs such as ascending myelitis, myositis, inflammatory myopathies; Hypothyroidism; Porphyria; Deficiency of vitamin B1 or B12; Critical illness polyneuropathy	**Age**: TPE: 39.7 ± 16.21; IVIG: 33.52 ± 18.40 **Female, n (%)**: TPE: 26 (48%); IVIG: 10 (37%) **Height**: NR **Weight**: NR **Disease severity**: Number of days between weakness and admission: TPE: 6.67 ± 4.6; IVIG: 5.68 ± 4.05	Plasma exchange (COM. TEC-9008021- Fresenius Kabi AG, Homburg, Germany), with 200–250 mL of plasma/ kg in five sessions (40–50 mL/kg per session). Participants were exchanged every other day within 7–14 days with replacement by fresh frozen plasma	IVIG (Immunoglobulin-G, Sk Plasma Co., Ltd., Seongnam, South Korea) in a dose of 0.4 g/Kg/day for five consecutive days	**Primary outcomes**: Score on GBS Disability Scale (GDS); Medical Research Council sum score (MRC sum score); Functional assessment of acute inflammatory neuropathy (FAAIN) in GBS score **Secondary outcome**: None
Maheshwari 2018, India RCT, parallel group Recruitment period: 2012–2014 *N* = 40 (TPE: 16; IVIG: 24)	Within 4 weeks of onset of progressive weakness; Bedridden or requiring ventilator support; GBS disability score grade 4 or 5	Any previous episode of GBS treated with steroids; Pregnancy; Previous treatment with either TPE or IVIG; Inability to pay for either of the two treatments; GBS disability score grade 1 to 3	**Age**: TPE: 34.81 ± 20.54; IVIG: 33.42 ± 14.072 **Female, n (%)**: Whole group: 13 (32.5%) **Height**: NR **Weight (kg)**: TPE: 54.88 ± 10.96; IVIG: 62.62 ± 13.22 **Disease severity**: Number of days before starting treatment: TPE: 5.88 ± 3.03; IVIG: 5.71 ± 3.8	5 x TPE (200–250 mL/kg, replacement fluid 5% human serum albumin and 0.9% normal saline ratio 80:20) were done on COBE Spectra cell separator version 7.0 (Terumo BCT, Lakewood, Colorado) over 7–14 days	400 mg/kg per day (total dose of IVIG 2 g/kg of body weight) for five consecutive days	**Primary outcomes**: Duration of hospital stay; Treatment related costs **Secondary outcomes**: Mean GBS disability score at 1, 2, 4 and 12 weeks
Van der Meché, 1992 The Netherlands RCT, parallel group Recruitment period: 1986–1989 *N* = 150 (TPE: 75; IVIG: 75)	Aged older than four years; Meets diagnostic criteria for acute Guillain-Barre syndrome; Unable to walk 10 m independently; Able to enter the study within two weeks of onset of the neuropathy	Previous episode of GBS Previous severe allergic reaction to properly matched blood products; Known selective IgA deficiency; Pregnancy; Treatment with immunosuppressive agents; Severe concurrent medical disease; Unavailability for follow-up during the next six months	**Age**: TPE: 48.8 ± 19.2; IVIG: 46.2 ± 19.3 **Female, n (%)**: NR **Height**: NR **Weight**: NR **Disease severity**: Days before starting treatment: TPE: median 1, range 0–4; IVIG: median 0, range 0–3	Exchange 200-250 ml of plasma per kg of body weight in 5 sessions within 7–14 days	0.4 g per kg of body weight per day for 5 subsequent days	**Primary outcomes**: Improvement by one or more grades on the functional scale at 4 weeks. **Secondary outcome**: Time to improve by at least one functional grade; Time to regain capacity for independent locomotion

Table 1 (continued)

Study ID trial design, recruitment period,	Inclusion criteria	Exclusion criteria	Age, Participant characteristics: *N*, age, disease severity	Details of TPE: interventions	Details of IVIG interventions	Study Outcomes
Ye 2015, China RCT, parallel group Recruitment period: 2006–2012 *N* = 67 (TPE: 33; IVIG: 34)	Age 16 years or older; Meets diagnostic criteria for GBS; Onset of neuropathic symptoms within the past 14 days	Atypical form of GBS, such as Miller-Fisher Syndrome; Serious pre-existing disease; Contra-indications to PLEX or IVIG	**Age**: TPE: 32.9 ± 7.8; IVIG: 31.5 ± 8.2 **Female, n (%)**: TPE: 11 (34%); IVIG: 13 (41%) **Height**: NR **Weight**: Body mass index: TPE: 24.5 ± 3.7; IVIG: 24.1 ± 3.6 **Disease severity**: Participants with limb activity disorder (n): TPE: 31; IVIG: 29; Participants with feeling disorder (n): TPE: 20; IVIG: 22; Participants with cranial nerve dysfunction (n): TPE: 13; IVIG: 15; Participants with weak or absent tendon reflex: TPE: 31; IVIG: 30; Participants with respiratory muscle obstacle: TPE: 1; IVIG: 2	5 × 50 mL/kg PEs to total exchange of 250 mL/kg during 8–13 day post-randomisation. (Replacement fluid = 1600 mL fresh frozen plasma, 20% albumin liquid (100 mL) + 400 mL ringer's solution. Overall, 10% of 10 mL calcium gluconate was added to each 1000 mL plasma complement; the first dose of heparin was 30–40 mg ordinary heparin anticoagulation; and the maintenance dose was l0–30 mg/h). If 5 PEs were inadequate [there were no changes in Hughes score and Medical Research Council (MRC) score and no improvement in breathing machine paralysis and bulbar paralysis for at least 1 week], a sixth exchange was administered to achieve a total exchange of 250 mL/kg	0.4 g/kg of human IVIG daily for 5 days commencing on day of randomization. One course of treatment only given if breathing difficulty improves in the patient and their condition becomes stable; otherwise, a second course of treatment is performed at an interval for 3 days. All patients were given vitamin B1, B12, ganglioside nerve nutrition, prevention of complications, support therapy and conventional treatments such as symptomatic treatment	**Primary outcomes**: Hughes score; MRC score **Secondary outcome**: "Curative effect of treatment" (definition NR); Laboratory indicators: IgG, IgA, IgM, C3, C4, MON%, Fib
CIDP						
Dyck 1994 USA RCT, crossover Recruitment period: NR *N* = 19 (TPE: 9; IVIG: 10 (only first phased is used in the analysis)	Diagnosis of CIDP, with static or worsening symptoms; Weakness score of at least 15 points	"Receipt of PE or IVIG in previous 6 weeks; Change in immunotherapy within previous 6 weeks; Diseases known to predispose to neuropathy (e.g. alcoholism, myxedema, diabetes mellitus, hepatic disease);"	**Age**: NR **Female, n (%)**: TPE: 5 (56%); IVIG: 4 (40%) **Height**: NR **Weight**: NR **Disease severity**: Neuropathic disability score: TPE: 94.8 ± 3.3; IVIG: 57.4 ± 29.0	Twice weekly plasma exchange (replacement fluid reconstituted crystalline albumin and citrate) for 3 weeks, followed by once weekly for 3 weeks	0.4 gm/kg IVIG (Gamimune, Miles Biological Products) once a week for 3 weeks, followed by 0.2 gm/kg once a week for the next 3 weeks. [Most patients treated at home].	**Primary outcome**: Change in Neuropathy Disability Score (NDS); NDS weakness subset; Summated compound muscle action potentials of ulnar, median, and peroneal nerves **Secondary outcomes**: Summated sensory nerve action potential of median and sural nerves; Vibratory detection threshold of the great toe, using CASE IV

Table 1 (continued)

Study ID trial design, recruitment period,	Inclusion criteria	Exclusion criteria	Age, Participant characteristics: *N*, age, disease severity	Details of TPE: interventions	Details of IVIG interventions	Study Outcomes
Zinman 2005 Canada RCT, parallel group Recruitment period: 2003–2004 *N* = 13 (IVIG 8; IA 5)	Diagnosed or probable CIDP; Physician judges a trial of immunotherapy would be beneficial	NR	**Age**: IA: 63.8 ± 9.3; IVIG: 63.5 ± 8.7 **Female, n (%)**: TPE: 0 (0%); IVIG: 3 (37.5%) **Height**: NR **Weight**: NR **Disease severity**: Average muscle score (AMS): TPE: 294 ± 12.3; IVIG: 273 ± 28.2	3 treatments over 7 days. A total of 3 plasma volumes were processed during each treatment. Plasma collection was performed by conventional plasmapheresis using a continuous flow apheresis device. The separated plasma was passed through a Citem10 immunoadsorption system at a rate of 15–35 ml/min. and the Citem10 device. No replacement fluid, other than small amounts of normal saline, was required	1 g/kg/day IVIG for 2 days	**Primary outcome**: Clinical Responder Status at 2 months post-treatment: Defined as stabilisation or improvement in at least 2/4 of: Average muscle score (AMS), grip strength, Toronto Clinical Neuropathy Score (TCNS), Hughes disability score **Secondary outcomes**: Determination of electrophysiological response status according to the following four measures: Summed sensory conduction velocities (SCV); Summed motor conduction velocities (MCV); Summed compound muscle action potential amplitudes (CMAP); Summed F-wave latencies (F). Electrophysiological response is defined as improvement in at least 2/4 measures in patients with stable disease, and as no deterioration or improvement in patients with progressive disease.

Abbreviations: *TPE* Therapeutic Plasma Exchange, *IVIG* Immunoglobulin, *N* Number of participants, *NR* Not reported, *SD* Standard deviation, *IgG* immunoglobin G, *IgA* immunoglobin A, *IgM* immunoglobin, *C3* Complement C3, *C4* Complement C4, *QMGS* Quantitative Myasthenia Gravis Score for disease severity, *AIDP* Acute inflammatory demyelinating polyradiculoneuropathy, *AMAN* Acute Motor Axonal Neuropathy, *AMSAN* Acute Motor Sensory Axonal Neuropathy, *MSS* Change in myasthenic muscular score

* Double filtration plasmapheresis: a two-step procedure where membrane plasma separation is followed by plasma filtration. Plasma filters of different mean pore sizes allow targeting preferred portions of plasma components such as autoantibodies and immune complexes

** Immunoadsorption: A selective method of therapeutic apheresis in which patient plasma, after membrane based or centrifugal separation from blood, is passed through an adsorber column which has a capacity to remove immunoglobulins and immune complexes by binding them to select ligands on the backing matrix surface of membranes or beads

†Australia, Belgium, Canada, Germany, Israel, Italy, Norway, Portugal, Switzerland, United Kingdom, USA

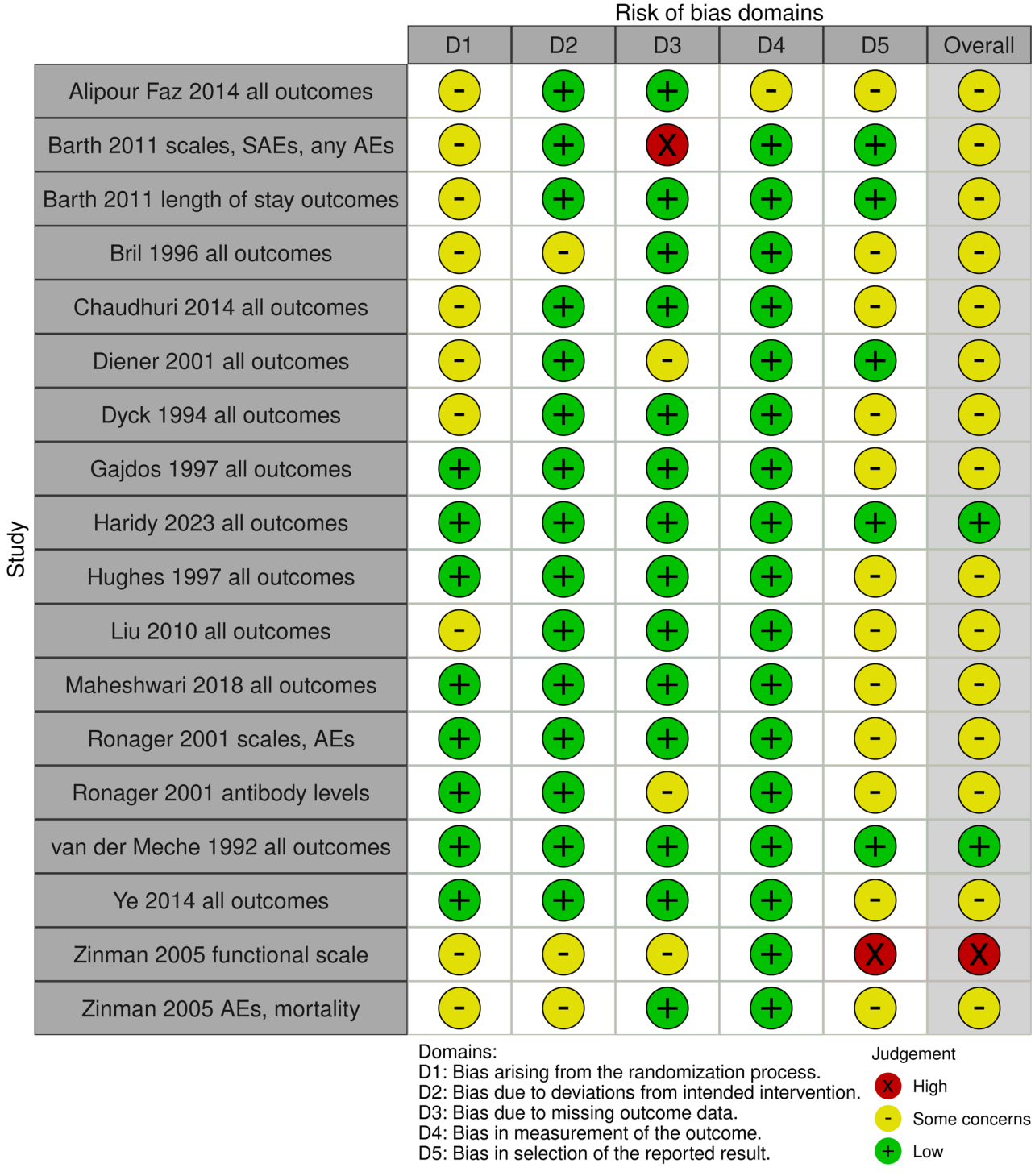

Fig. 2 ROB2 summary

Review primary outcomes

For improvement on functional scales at up to three weeks, there was no significant difference between TPE versus IVIG at three weeks (SMD 0.31 (95% CI -0.01 to 0.64, low-certainty evidence, 3 RCTs [19, 24, 27] Table 2); and at a later time point-three to six weeks there was also no significant difference (SMD 0.42, 95% CI -0.01 to 0.85, low-certainty evidence, 1RCT [19] Table 3). No trials measured the changes in functional scale at any later time point (Table 4).

Two trials [24, 27] reported on time to improvement of one point on functional scale (Table 5) and in both trials,

Table 2 Functional scales up to week 3

Study ID	Scale	Outcome definition, time of assessment	TPE	IVIG
Myasthenia Gravis				
Barth 2011	QMGS[1]	Change in QMGS from baseline to 21 days, expressed as number of points of improvement	Mean 5.3, SD 5.5 (*N* = 43)	Mean 3.3, SD 3.6 (*N* = 41)
	% decrement in repetitive nerve stimulation	At 21 days	12% (*N* = 43)	9.2%(*N* = 41)
	Jitter, microseconds	At 21 days	Mean 83.6 (*N* = 43)	Mean 75.3 (*N* = 41)
	Abnormal pairs %	At 21 days	57.3% (*N* = 43)	52.5% (*N* = 41)
	Blocking pairs %	At 21 days	13.6% (*N* = 43)	8.8% (*N* = 41)
Gajdos 1997	Myasthenic muscular score (0-100) (100 is normal)	Myasthenic muscular score (0-100) (100 is normal), at 15 days	Mean 16.6, 95%CI 11.6, 21.6 (*N* = 41)	Mean 15.6, 95%CI 10.9, 20.3 (*N*=-46) IVIg for 5 days group Mean 12.4 95%CI 5, 19.8 (*N* = 23) IVIg for 3 days group Mean 18.9, 95%CI 13.1, 24.7 (*N* = 23)
	Myasthenic muscular score (0-100) (100 is normal)	Number of participants who reached a 20-point gain in score on the myasthenic muscular score within 15 days	*n* = 26, *N* = 41	*n* = 22, *N* = 46 IVIg for 5 days group *n* = 8, *N* = 23 IVIg for 3 days group *n* = 14, *N* = 23
	Myasthenic muscular score (0-100) (100 is normal)	Number of participants who reached a 20-point gain in score on the myasthenic muscular score at 15 days	*n* = 18, *N* = 41	*n* = 18, *N* = 46 IVIg for 5 days group *n* = 7, *N* = 23 IVIg for 3 days group *n* = 11, *N* = 23
Liu 2010	QMG score	QMG score post-treatment (at 14 days)	DFPP group Mean 10.9, SD 3.1, N = *15 (used in the meta-analysis)* IA group Mean 8.9, SD 0.7, *N* = 10	Mean 12.5, SD 1.0, *N* = 15
		Time to Remission (days). Remission is defined as relative score above 25%.	DFPP group Mean 6.70, SD 0.34, *N* = 15 IA group Mean 5.38, SD 0.42 *N* = 10	Mean 8.4, SD 1.54, *N* = 15
	Clinical efficacy rate at 14 days. Clinical efficacy was defined as relative score above 50% improvement from baseline	At 14 days		
Ronager 2001	QMGS -quantified MG clinical score electromyogram (EMG)[4]	Week 1	Mean 0.23, *N* = 4	Mean 0.1, *N* = 8
Guillain-Barre Syndrome				
Haridy 2023	MRC sum score[5] *(Included in the meta-analysis)*	10 days	Mean 37.09, SD 16.87, *N* = 54	Mean 41.15, SD 11.53, *N* = 27
	GBS disability score[6]	10 days	Mean 3.35, SD 1.07, *N* = 54	Mean 3.04, SD 1.26, *N* = 27
	Functional assessment of acute inflammatory FAAIN[7]	10 days	Mean 3.93, SD 1.62, *N* = 54	Mean 4.33, SD 1.21, *N* = 27
Ye 2014	Neural function deficit scale	Week 1	Mean 3.12, SD 0.81, *N* = 32	Mean 3.37, SD 0.78, *N* = 32
		Week 2	Mean 2.03, SD 0.95, *N* = 30	Mean 2.56, SD 0.93, *N* = 29
	MRC scale *(included in the meta-analysis)*	Week 1	Mean 23.56, SD 7.25, *N* = 32	Mean 21.03, SD 6.73, *N* = 32
		Week 2	Mean 29.59, SD 10.73, *N* = 30	Mean 24.62, SD 10.51, *N* = 29

Table 3 Functional scales 3 to 6 weeks

Study ID	Scale	Outcome definition, time of assessment	TPE	IVIG
Myasthenia Gravis				
Barth 2011	QMGS	Reported as improvement in QMGS from baseline to 28 days	Mean 4.7, SD 5.7 ($N=43$)	Mean 2.6, SD 4.0 ($N=41$)
	% decrement in repetitive nerve stimulation	At 28 days	13.40% ($N=43$)	6.5% ($N=41$)
	Jitter, microseconds	At 28 days	97.70%, ($N=43$)	72.60%, ($N=41$)
	Abnormal pairs %	At 28 days	67.90%, ($N=43$)	47.60%, ($N=41$)
	Blocking pairs %	At 28 days	16.40%, ($N=43$)	7.10%, ($N=41$)
Guillain-Barre Syndrome				
Bril 1996	Disability grade	At 1 month	Mean 3.1, SD 0.3, $N=18$	Mean 2.6, SD 0.2, $N=26$
Chaudhuri 2014	Hughes Grade	Number of people at each Hughes Grade	$N=18$ Grade 0 $n=5$ Grade 1 $n=5$ Grade 2 $n=3$ Grade 3 $n=1$ Grade 4 $n=1$ Grade 5 $n=1$ Grade 6 $n=2$	$N=19$ Grade 0 $n=4$ Grade 1 $n=6$ Grade 2 $n=6$ Grade 3 $n=2$ Grade 4 $n=0$ Grade 5 $n=0$ Grade 6 $n=1$
Haridy 2023	MRC sum score	1 month	Mean 44.75, SD 16.16, $N=51$	Mean 51.46, SD 8.68, $N=26$
	GBS disability score	1 month	Mean 2.59 SD 1.47	Mean 1.81 SD 1.52
	Functional assessment of acute inflammatory FAAIN	1 month	Mean 2.76, SD 1.93, $N=51$	Mean 2.59, SD 1.63, $N=26$
Hughes 1997	Disability grade	4 weeks	Mean 0.9, SD 1.3, $N=121$	Mean 0.8, SD 1.3, $N=130$
Maheshwari 2018	Hughes Grade	Week 4	Mean 3.56, SD 1.31, $N=16$	Mean 3.04, SD 1.2, $N=24$
van der Meche 1992	Number of people improved by one grade on a functional score 0–6 where 0 is healthy and 6 is dead. This was cross-referenced with the MRC scores for six bilateral muscle groups from 60 (normal) to 0 (quadriplegic) with a high level of agreement.	Week 4	$N=73$, 34% n=25improved	$N=74$, 53% $n=39$ improved
Chronic inflammatory demyelinating polyradiculo-neuropathy (CIDP)	No data			
Dyck 1994	"Neuropathy Disability Score (NDS) (Scoring: Enter 0 for no deficit, 1 for mild deficit, 2 for moderate deficit, 3 for severe deficit, and 4 for complete absence of function or severest deficit).(0-100) increase scores indicate better symptoms "	6 weeks	Mean 83, SD 40, $N=9$	Mean 68, SD 28, $N=10$
	NDS-W (Weakness score)	6 weeks	Mean 63, SD 36, $N=9$	Mean 51, SD 27, $N=10$
	"Summated compound muscle action potential ""The neurological disability score summates all neuropathic deficits of weakness, scored as 1 (25r/c), 2 (SO%), 3 (7557 weak), or 4 (paralyzed) considering the identity of the muscle and age, sex, and physical fitness of the patient"" from the figure score 0–10 (MV) increases in score is better"	6 weeks	Mean 7.9 MV (mille volte) SD 6.1, $N=9$	Mean 5.2 (MV), SD 1.9, $N=10$

Table 4 Functional scales at 12 weeks

Study ID	Scale	Outcome definition, time of assessment	TPE	IVIG
Myasthenia Gravis	No data			
Guillain-Barre Syndrome				
Chaudhuri 2014	Hughes Grade	Number of people at each Hughes Grade at 60 days	*N* = 16 Grade 0 n-8 Grade 1 *n* = 3 Grade 2 *n* = 4 Grade 3 *n* = 1 Grade 4 *n* = 0 Grade 5 *n* = 0 Grade 6 *n* = 0	*N* = 17 Grade 0 *n* = 9 Grade 1 *n* = 3 Grade 2 *n* = 4 Grade 3 *n* = 1 Grade 4 *n* = 0 Grade 5 *n* = 0 Grade 6 *n* = 0
Maheshwari 2018	Hughes Grade	Change in GBS-DS from baseline at week 12	Mean 2.29, SD 1.4, *N* = 16	Mean 2.73, SD 1.34, *N* = 24
Haridy 2023	MRC sum score[5]	3 months	Mean 47.92, SD 16.77, *N* = 51	Mean 55.38, SD 7.01, *N* = 26
	GBS disability score[6]	3 months	Mean 1.85, SD 1.94, *N* = 51	Mean 1.15, SD 1.59, *N* = 26
	Functional assessment of acute inflammatory FAAIN[7]	3 months	Mean 2.11, SD 2.32, *N* = 51	Mean 1.52, SD 1.91, *N* = 26
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	No data			
Zinman 2005	Summed sensory conduction velocity	2 months (Nerve conduction study changes Units m/s)	Mean plus 7.7 SD 15.6, *N* = 5	minus 6.7, SD 19.2, *N* = 7
	Summed motor conduction velocity	2 months (Nerve conduction study changes Units m/s)	Mean plus 3.1, SD 5.9, *N* = 5	plus 13.8, SD 103.9, *N* = 7
	Summed compound muscle action potential	2 months (Nerve conduction study changes Units m/s)	Mean plus 0.5, SD 3.0, *N* = 5	minus 1.1, SD 2.1, *N* = 7
	F-wave latency (Table 4)	2 months (Nerve conduction study changes Units m/s)	Mean minus 21.1, SD 48.2, 5	plus 12.3, SD 38.7, *N* = 7

Table 5 Time to improvement one scale point

Study ID	Scale	Outcome definition	TPE	IVIG
Myasthenia Gravis				
Gajdos 1997	Myasthenic muscular score	Response Time (time to treatment response, i.e., to reach a 20-point gain in score	Median time to response 9 days (*n* = 26)	Median time to response > 15 days in the IVIG group (*n* = 22)
		Relative risk of response by day 15	RR 0.67 (95% CI 0.38, 1.18) *n* = 41 [26 responders]	RR 2.01 (95% CI: 0.84, 4.80) *n* = 46
		Number of participants who still had an increase in score of 20 points or more at day 15	18/41	18/46
Liu 2010	QMG score	Time to remission (days). Clinical remission was defined as relative score above 25% and clinically effective was above 50%.	DFPP (double filtration and plasmapheresis) group: mean 6.70 SD 0.34 (*n* = 15) IA (immunoadsorption) group: mean 5.38 SD 0.42 (*n* = 10)	Mean 8.4 SD 1.54 (*n* = 15)
Guillain-Barré Syndrome				
Bril 1996	Disability grade	Number of days to improve by 1 disability grade	mean 36 SD 10 (median 16.5 days), *n* = 18	mean 39 SD 12 (median 14) *n* = 26
		Time to reach disability grade 1 (days)	mean 127 SD 37 *n* = 7	mean 100 SD 27 *n* = 16
Hughes 1997		Median days to unaided walking	Median (IQR) 49 (19–148) (*n* = 121)	51 20–164) (*n* = 130)

time to improvement was longer for the IVIG group. In one trial [24], the median response time (defined as a 20 point gain on the myasthenic muscular score) was 5 days in the TPE group versus > 15 days in the IVIG group. In one trial [28], the DFPP group had a mean time to remission of 6.70 days, compared to 8.9 days for the IA group and 8.4 days for IVIG group.

One trial [19] measured quality of life outcomes, with participants showing a greater, but not statistically significant, improvement, in the TPE group than in the IVIG

group on the QoL60 scale at three weeks (MD -7.00, 95% CI -20.94 to 6.94 very low-certainty evidence Table 6) and a greater improvement in the IVIG group at three to six weeks (MD 6.00 95% CI -7.81 to 19.81 very low-certainty evidence Table 7). On the MG-QoL15 scale TPE was favoured, but not statistically different, at 3 weeks (mean – 1, 95%CI -5.73 to 3.73 very low-certainty evidence Table 6), whereas IVIG was favoured at 3–6 weeks with a mean of 4 points improvement (95%CI -0.21 to 8.21 very low-certainty evidence Table 7).

One trial [19] reported SAEs with no difference between TPE and IVIG (OR 1.95 95% CI 0.17 to 22.38, 84 participants very low-certainty evidence Table 8). Pooled data from two trials [24, 29] 30 showed no difference on the AE occurrence at any grade (OR 1.53 95% CI 0.03 to 69.74, 111 participants, very low-certainty evidence Table 9).

Review secondary outcomes

Two trials [18, 27] reported a shorter hospital stay duration in the TPE group, however the evidence for this is very uncertain and the difference was not statistically significant (MD -2.22, 95% CI -5.60 to 1.16, 2 RCTs [18, 27], 54 participants, very low-certainty evidence Table S3A). One trial [19] reported none of the participants required hospitalisation/ intubation by day 14. The length of intubation was similar in an another trial [18] with a median of 13 h in the TPE group (range 2-216) and 12 h in the IVIG group (range 2–22). One trial [27] reported the number of participants who required ventilator support; two (13%) in the DFPP group, one (10%) in the IVIG group versus six (40%) for TPE (Table S3C). There was no significant difference in the circulating AChR antibodies between TPE vs. IVIG ($p = 0.36$) at day 15 in one trial [24]. In one trial [29], rapid decrease in IgG and IgM by 83% and 86% respectively was seen at week one after TPE whereas the IgG plasma level was increased in average by 159% in the IVIG in week one with no changes in IgM. At week 4, IgG and IgM remained decreased in the TPE by 18% and 16%, receptively and an increase by 43% in the IVIG [29]. Similarly, TPE was significantly better in clearing pathogenic antibodies than IVIG in one trial [27] and the difference was statistically significant as Titin-ab, AChR-ab, and PrsmR-ab were significantly decreased ($P < 0.05$) for both DFPP and IA groups compared to the IVIG group.

None of the included trials reported on mortality at one year (See Supplementary table S2B).

Table 6 Health-related quality of life up to three weeks

Study ID	Scales	Scale definition	TPE	IVIG
Myasthenia Gravis				
Barth 2011	MG-QoL60 scale	Change from baseline in MG-QoL60 scale at day 21	Mean – 18 SD 27 ($n = 30$)	Mean – 11 SD 29 ($n = 32$)
	MG-QoL15 scale	Change from baseline in MG-QoL15 scale at day 21	Mean – 8 SD 9 ($n = 30$)	Mean – 7 SD 10 ($n = 32$)

Table 7 Health-related quality of life at 3–6 weeks

Study ID	Scales	Scale definition	TPE	IVIG
Myasthenia Gravis				
Barth 2011	MG-QoL60 scale	Change from baseline in MG-QoL60 scale at day 28	Mean – 17 SD 23 ($n = 30$)	Mean – 23 SD 32 ($n = 32$)
	MG-QoL15 scale	Change from baseline in MG-QoL15 scale at day 28	Mean – 5 SD 5 ($n = 30$)	Mean – 9 SD 11 ($n = 32$)

Review costs

One RCT, conducted in 2011 [19], published a cost analysis [38], finding that the mean of the total cost in the TPE group was £4609.36 while in the IVIG group it was £6107.69. Therefore, the mean of the total cost per patient in the IVIG group were £1,498.33 greater than those in the TPE group. This research incorporated hospital costs, costs of blood products, and physician costs. The majority of costs in the TPE group were associated with hospital costs, while the largest proportion of costs in the IVIG group were related to blood product costs. The hospital costs in the TPE group were £ 340.76, which was higher than the IVIG group's costs of £ 1068.55. Physician costs were higher in the TPE group than the IVIG group (£137.56 vs. £23.62). Conversely, the costs associated with blood products in TPE arm were lower than in the IVIG arm (£1070.04 vs. £5015.38).

Review economic evaluation modelling

Two different Markov models were identified for patients with MG in Canada [39], the United Kingdom [40], and the United States [41]. Two studies [39, 40] developed a Markov model including 4 health states based on the myasthenia gravis activities of daily living (MG-ADL) total score (MG-ADL below 5, MG-ADL 5 to 7, MG-ADL 8 to 9, and MG-ADL 10 or more) to capture disease severity, as well as crisis and death health states. However, another study [41] utilised the Quantitative Myasthenia Gravis (QMG) score with 4-week cycles as a foundation for constructing a Markov model. In this study, QMG classification was preferred to the MG–ADL, as it appears to have less of a floor effect and would therefore better characterize improvements in a patient with low baseline scores. Further detail can be found in Appendix E.

The studies evaluated the utility score and the disutility associated with AEs, which encompassed the disutility of MG-related hospitalizations and emergency department visits. Both studies calculated the costs associated with AEs and treatment, with one study additionally

Table 8 Serious adverse events (SAEs)

Study ID	Definition of AEs	TPE	IVIG
Myasthenia Gravis			
Barth 2011	Reported as serious AEs	Number of people with event $n=2$, $N=43$	Number of people with event $n=1$, $N=41$
Guillain-Barre Syndrome			
Chaudhuri 2014	Need for ventilator support	Number of event $n=7$, $N=18$	Number of event $n=9$, $N=19$
Diener 2001	TPE: Death, Rupture of liver and spleen IVIG: Absolute arrhythmia, tachycardia, chills, temp. rise, short breath Total events:11 with no details for each group	Number of event = not reported, $N=26$	Number of event n = not reported, $N=23$
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	No data		
Zinman 2005	No AEs	$n=0$,$N=8$	$n=0$, $N=5$

Table 9 Any adverse events (AEs)

Study ID	Type of AEs	TPE	IVIG
Myasthenia Gravis			
Gajdos 1997	Patients with at least one event	Number with event = 8, $N=41$	Number with event $n=0$, $N=46$
Ronager 2002	Any AEs	Number with event $n=5$, $N=12$	Number with event $n=9$, $N=12$
Guillain-Barre Syndrome			
Haridy 2023	Number of participants with complications of therapy	Number with event = 4, $N=54$	Number with event = 2, $N=27$
Hughes 1997	Treatment curtailed because of side-effects	Number with event = 3, $N=121$	Number with event = 2, $N=130$
van der Meche	Any AEs	Number with event = 68,$N=73$	Number with event = 39,$N=74$
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	No data		
Zinman 2005	Rash, resolving with hydrocortisone	Number with event = 0, $N=5$	Number with event = 2, $N=13$
	Mild to moderate headache, resolved with over the counter analgesics	Number with event = 2, $N=5$	Number with event = 2, $N=13$

evaluating indirect costs, including productivity loss from patients and their caregivers. However, there are gaps in outputs reported in included RCTs for economic evaluation modelling that should be considered (Further detail can be found in Appendix F).

Therapeutic plasma exchange (TPE) versus intravenous immunoglobulin (IVIG) for GBS

Description of included studies

Eight RCTs were included one from each of the following countries Canada [20], Germany [22], Egypt [25], The Netherlands [30], China [31], two from India [21, 28] and one was international.26 The total plasma volume of 200 to 250 ml/kg exchanged was given over 5 cycles for 5–10 days. For the IVIG group, IVIG was given at 0.4 to 0.5 g/kg/day for consecutive 5 days was given across all RCTs. Hughes and GBS scales were used to assess disability at randomisation (see Table 1).

Risk of bias

Two trials [25, 30] were at low RoB across all domains. All other six trials had some concerns, most commonly due to lack of published trial registration (5/8) [21, 22, 27, 29, 32], or due to no description of randomisation and allocation concealment. (3/8) [21–23] (see Fig. 2).

Review primary outcomes

Two trials [26, 32] measured improvement in strength using Medical Research Council sum score (MRC), there was no significant difference between TPE and IVIG at three weeks (SMD – 1.22, 95% CI -3.13 to 0.69, very low-certainty evidence, I^2 >90% Table 2). There was a significant heterogeneity as one trial [31] favoured IVIG and one [25] reported no difference between TPE and IVIG. At three to six weeks, no significant difference was found between TPE vs. IVIG (SMD – 0.65 95% CI -1.40 to 0.11, 4 RCTs [20, 25, 26, 28] low-certainty evidence, I^2 >90% Table 3). At up to 12 weeks, no difference was found (SMD 0.06, 95% CI – 0.61 to 0.74, 2 RCTs [25, 28], very low-certainty evidence Table 4).

For time to improvement by one point on the GBS disability grade, one trial [20] reported no significant difference with a median of 16.5 days in the TPE group vs. 14 days for IVIG. Also, one study [26] reported no difference

with a median of 49 days for unaided walking in the TPE group vs. 51 days for the IVIG group. (Table 5)

One study [20] reported SAEs as the need for ventilation with no difference between TPE and IVIG (OR 0.71 95% CI 0.19 to 2.61, 1 RCT, 37 participants, very low-certainty evidence Table 8). There was no difference in the number of AEs at any grade between TPE vs. IVIG (OR 1.27 95% CI 0.36 to 4.48, 2 RCTs [25, 26], 332 participants, very low-certainty evidence Table 9). A summary of all reported outcomes for all included trials is available in Supplementary Table S2A.

Review secondary outcomes

There was no significant difference between TPE and IVIG regarding hospital stay length (MD 1.44, 95% CI -2.94 to 5.83, 2 RCTs [25, 28] TableS3A) There was no difference in the proportion of patients needing ICU admission between TPE ($N=42$, 77.8%) vs. IVIG ($N=16$, 59.3%), and in intubation duration (MD 1.09, 95% CI -4.14 to 6.32, 1 RCT [25], 81 participants Table S3C). No difference was found in mortality at one year (OR 1.21, 95% CI 0.49 to 2.95, 6 RCTs [20–22, 25, 26, 30], 567 participants, Table S3F).

One trial [26] reported on time to return to work with a median of 290 days for the TPE group and a significantly longer median time of 371 days for the IVIG group. One trial [31] found that both TPE and IVIg reduced blood immunoglobulin IgG, IgA, IgM, C3 and C4, but these were significantly lower in the TPE group compared to the IVIg group. Quality of life was not measured in any of the included trials.

Review cost

One study [21] found that the average total cost in the IVIG group was £3960.52, which was higher than the £2334.16 reported in the TPE group (Difference= £1,626.36). In this study, the total costs were divided into two sections, including treatment costs and costs of other expenditures. Mean treatment cost in IVIG group was about twice of this cost in TPE group (£2714.38 in IVIG vs. £1362.47 in TPE). The average cost of other expenditures in the IVIG group was £1248.68, which was higher than the £ 1012.96 recorded in the TPE group.

Another study [28] assessed both health system costs and out-of-pocket (OOP) expenditures using a bottom-up costing approach. The median of the total cost for treating a patient with GBS was found to be £4149.11 and £2707.05 when utilizing IVIG and TPE, respectively. Therefore, the median of the total costs per patient in the IVIG group were £1,442.06 higher than those in the TPE group. The median of the total OOP expenditure in IVIG group was £3647.35 and in TPE group was £1731.28. The most significant cost category for both groups was the cost associated with the procedure. The median cost associated with the IVIG procedure was £3243.93, while the median cost for the TPE procedure was £1495.59 (Table S3G).

Review economic evaluation modelling

A research study [42] developed a decision tree model to evaluate the cost-effectiveness of IVIG compared to TPE in the treatment of patients diagnosed with GBS. In this research, the findings from two clinical trials [26, 30] were utilized to evaluate the effectiveness of the comparators. Since these two studies determined that there was insufficient evidence to suggest one therapy was more effective than the other, a cost minimization analysis was performed. In this study, improvement in disability grade 4 weeks after randomization was used as an outcome. For costing, cost of supplies, professional costs, overhead costs and hotel costs, capital costs, imputed costs were assessed. Further detail can be found in Appendices E and F.

Therapeutic plasma exchange (TPE) versus intravenous immunoglobulin (IVIG) for CIDP

Description of included studies

Two trials were included [23, 32] from USA [23] and from Canada [32]. Both included a small sample size of 20 patients each. (see Table 1) In one study [23], TPE was given twice for 3 weeks, followed by only weekly for 3 weeks. IVIG was at 0.4 g/kg IVIG once a week for 3 weeks, followed by 0.2 g/kg once a week for the next 3 week. In the other study [32], IVIG was given over two days every month at 1 g/kg/ for six cycles. Patients were randomly assigned to receive monthly treatments of either immunoadsorption (IA) with the staphylococcal protein A column or IVIG (1 g/kg/day × 2 days) for a period of 6 months.

Risk of bias

One trial [32] was at overall high RoB owing to incomplete outcome reporting. One study [23] had some concerns, as it was unclear how allocation concealment had been achieved, and there was no prospective trial registration or protocol. (see Fig. 2).

Review primary outcomes

No trials reported functional scale scores at three weeks. One trial of 19 participants [23] reported neuropathy disability score at six weeks. Participants in the IVIG group showed a lower level of deficit at 6 weeks on the modified Neuropathy Disability Score (NDS) (lower values indicated better improvement) for the TPE group with no significant difference (MD 15.00, 95% CI -16.37, 46.37, 1 RCT, very low-certainty evidence Table 2). One trial of 12 participants [32] reported summed sensory conduction velocity at two months with no significant

difference between the groups (MD 1.00, -18.73, 20.73 1 RCT, very low-certainty evidence Table 2). The same trial [32] reported no SAEs in either of the groups and only two instances of AEs in each group. The same trial [32] also reported AEs at any grade, but only per event, rather than per outcome. No trials reported on quality of life.

Review secondary outcomes

No study reported on duration of hospital stay, ICU stay or intubation. One study [32] reported two deaths unrelated to treatment in the IVIG arm.

Review cost

No studies reported cost data.

Review economic evaluation modelling

One study [43] used a Markov model with 12-week cycles to compare the cost effectiveness of IVIG vs. corticosteroid for the treatment of patients with CIDP. This Markov model incorporates health states such as IVIG initial treatment, IVIG responder, IVIG non-responder, corticosteroids (no AEs), fracture, diabetes, glaucoma, cataract, infection, and death. The parameters considered included IVIG response rate, IVIG relapse rates, corticosteroid adverse event rates, mortality rates, and utility values associated with treatments and AEs. In this model, the AEs associated with steroid use such as fractures, diabetes, glaucoma, cataracts, and serious infections were incorporated. Another study conducted in Thailand [44] employed a Markov model with six health states: initial treatment, no response/relapse, no response after additional IVIG or immunosuppressants, remission, disability, and death. This study evaluated both direct medical costs and direct non-medical costs. Further detail can be found in Appendix D. We also showed the existing gaps between outcomes needed for economic evaluation and outcomes reported in included RCTs (Further detail can be found in Appendix F).

Discussion

Autoimmune neurological conditions are amongst the most common conditions to be treated with TPE and IVIG. Given the high cost of these interventions and healthcare utilisation by patients with these conditions, an overall effectiveness, safety and economic analysis is important for guiding treatment.

In this systematic review, we included evidence from 15 trials from 1992 to 2023 on the use of TPE vs. IVIG for treating autoimmune neurological disorders. Eight trials were on GBS, 5 on MG and only two on CIDP. No trials were found for other autoimmune neurological disorders despite our search terms including a much wider list of conditions. All of the trials were parallel in design. The trials included 12 to 383 participants and used a range of different methods to assess outcomes. They were at low to high RoB, with two trials [19, 32] being at high RoB in at least one domain. There is an evidence gap for CIDP, although it is one of the commonest reasons that IVIG is administered in the UK, with trials being too small to give definitive efficacy endpoints. Meta-analysis was not possible for all of the reported outcomes due to the diverse range of outcome measurements used for reporting clinical outcomes.

Overall, we found TPE and IVIG may have equal effectiveness for improving symptoms of MG, GBS and CIDP, with TPE perhaps showing better results in directly removing/decreasing the circulation antibodies. However data were limited, especially for CIDP. The AE profile appeared to be similar for both treatments as did hospital stay and time spent intubated. However data are limited, and only one trial in MG reported quality of life outcomes.

Time to return to work appeared to be longer for the TPE group than IVIG, although the evidence was limited as it came from only one trial. In general, the clinical follow-up was short (3–6 weeks) across the included trials. Given that these disorders are chronic conditions with progressive/relapse nature, a longer rather than short clinical assessment is needed to ascertain any meaningful differences between the TPE and IVIG especially as the duration of effectiveness of these treatments and the frequency of administration may vary.

Evidence from this review showed both treatments may be equally effective and safe for treating autoimmune neurological disorders. These results broadly concur with the outcomes of other systematic reviews. One review [45] including 10 studies of MG and 14 GBS studies including evidence from both RCTs and non-RCTs and concluded that TPE and IVIG did not differ in their effectiveness or safety. Evidence from another review [46] concluded that IVIG alone did not improve the clinical outcomes or mortality in COVID-19 related GBS and TPE should be considered as one of the treatments. Evidence from a Cochrane review concluded that TPE should be deliberated as the first line of treatment before IVIG in GBS [47]. Another review [48] found the response rates to TPE treatment were greater than IVIG on MG disease severity scales.

As effectiveness and safety data appeared similar for both treatments, overall healthcare costs are an important outcome for guiding use of IVIG or TPE.

Our results are consistent with other assessments of the cost effectiveness of plasma exchange compared to IVIG. A cost-minimisation analysis [49] of 44 patients with autoimmune neurological disorders conducted from May 2019 to May 2020 in a single centre study in the UK reported that TPE was 50% less expensive than IVIG.

[49] This analysis included factors such as staffing, capital equipment, consumables, volumes of TPE used, and compared it to the cost of an equivalent treatment strategy using IVIG. An advantage of our analysis over this is that it includes data from a wide range of trials and incorporates the assessments of effectiveness, AEs and economic analysis.

Recommendations for practice and research

The low incidence of these disorders may preclude conducting larger RCTs and so the data included in this meta-analysis is likely to provide the bulk of evidence to guide future practice. Large scale data collection using a shared platform that collects ongoing data from all study designs including data retrieved from data linkage would be an effective way of guiding future treatment considerations. The proposed platform could also have information related to the diagnosis of these disorders such as different biomarkers, tissue samples and other tests in addition to systematically documenting different treatments regimen and their side effects. It is important when designing future trials that patients' age and comorbidities are taken into account, and trials should be conducted in both inpatient and outpatient settings.

The analysis was limited by lack of data required for a full economic analysis and we recommend that future trials should include additional outcomes data including quality of life measures, time to return to work, care needs and support. A standardised way of measuring and reporting on clinical improvement would also be beneficial. The long-term effectiveness and safety of these treatments are not yet clear and following participants for a prolonged period is a necessity.

While the review question is appropriately broad, the 11 randomized studies included are limited to myasthenia gravis, Guillain–Barré syndrome, and chronic inflammatory demyelinating polyneuropathy (CIDP), and pooling data across these conditions is inherently challenging. This reflects fundamental differences in disease acuity, course, recovery, and progression. In particular, myasthenia gravis and Guillain–Barré syndrome are acute conditions in which short-term recovery outcomes are more readily captured, whereas CIDP requires longer follow-up and different outcome measures/scales and time points to adequately assess disease progression.

Based on the published randomised controlled trials, TPE and IVIG appear equivalent in effectiveness for the treatment of autoimmune neurological disorders. Given the high cost of IVIG (£133,580,863 per year in the UK), the potential for TPE to be used in its place when models have found it to be 50% less expensive, would provide a safe, effective and more cost-effective treatment for patients and for health services.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

Catherine Kimber - wrote the protocol, screened all citations, extracted data, collated and analysed data, undertook risk of bias assessments and GRADE assessments, contributed to the writing of the manuscript. Reem Malouf - edited the protocol, screened citations, extracted data, collated and analysed data, undertook risk of bias assessments and GRADE assessments, contributed to the writing of the manuscript. Javad Javan - searched for health economic data, conducted the health economic analysis, contributed to the writing of the manuscript. Carolyn Dorée - developed the original search strategy, searched for trials, screened citations, edited and agreed the manuscript. Elaine Howe - reviewed the protocol, commented on our chosen outcomes and read and commented on the final manuscript. Vickie McDonald - edited and commented on the manuscript. M Isabel Leite - agreed the protocol, advised on outcomes, interpreted the analysis, edited and commented on the manuscript. Simon Rinaldi - interpreted the analysis, edited and commented on the manuscript. Apostolos Tsiachristas - advised on health economic outcomes, searched for health economic data, conducted the health economic analysis, contributed to the writing of the manuscript. Michael Desborough - interpreted the analysis, edited and commented on the manuscript. Lise Estcourt - agreed the protocol, interpreted the analysis, edited and commented on the manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

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