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SUMMARY WITH CRITICAL APPRAISAL

Off-Label Use of Intravenous Immunoglobulin for Neurological Conditions: A Review of Clinical Effectiveness

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Context and Policy Issues

Immunoglobulin (also known as immune globulin or gamma globulin) is composed of IgG, an antibody and constituent of the adaptive human immune system.[1,2] The fractionated blood product intravenous immunoglobulin (IVIG) contains concentrated IgG and plasma from thousands of donors.[1-5] Health Canada has licensed its use or "on-label" use for treatment of: allogenic bone marrow transplantation;[1-3,5,6] chronic B-cell lymphocytic leukemia;[1,4-6] common variable immune deficiency;[2] congenital agammaglobulinemia;[2] dysgammaglobulinemias such as mucocutaneous candidiasis and hyper-IgE;[2] Guillain-Barré syndrome (in adults) including Miller-Fisher syndrome and other variants;[5,7] hypogammaglobulinemia;[2] idiopathic thrombocytopenic purpura;[1,2,4,5,7] multifocal motor neuropathy;[5,7] pediatric HIV infection;[1,2,4,6] primary and secondary immunodeficiency diseases;[1,4-7] and X-linked immunodeficiency with hyper-IgM.[2]

However, in addition to its immunogenic properties, IVIG produces anti-idiotype antibodies, inhibits the complement pathway, modulates Fc receptors on macrophages and other cells, suppresses pathogenic cytokines, modulates adhesion molecules which affects cell migration, modulates T-cells, and directly affects remyelination.[8] These potential effects have led to an increase in "off-label" use of IVIG to treat an array of neurological and neuromuscular conditions such as: acute disseminated encephalomyelitis;[1,2,4,5] adrenoleukodystrophy;[1,4,7] amyotrophic lateral sclerosis;[1,2,4,5,7] autism;[1,4,7] chronic inflammatory demyelinating polyneuropathy;[1,2,4] critical illness polyneuropathy;[1,4,7] diabetic neuropathy;[1,4] encephalitis;[2] epilepsy;[2,5] Guillain-Barré syndrome (in children);[1,2,4] inclusion body myositis;[1,2,4,5,7] intractable childhood epilepsy;[1,4,7] multiple motor neuropathy;[1,2,4] multiple sclerosis;[1,2,4,5] myasthenia gravis including Lambert-Eaton myosthenic syndrome;[1,2,4,5,7] opsoclonus-myoclonus;[1,2,4] paraproteinemic neuropathy;[1,4,7] pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections;[1,4,5] polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes syndrome;[1,4,7] polymyositis and dermatomyositis;[1,2,4,5] Rasmussen's encephalitis;[1,4,5] stiff person syndrome;[1,2,4,5] and transverse myelitis.[2]

Between 1998 and 2006, Canada's per capita use of IVIG grew 115%, which makes Canada one of the highest consumers of IVIG per capita worldwide.[1,3,4] The belief is that much of this growth is attributable to an increase in off-label use of IVIG.[1,2,4] A three month audit in 2007 conducted by Ontario Regional Blood Coordinating Network found that: 50% of IVIG use was on-label; 40% was off-label, but potentially clinically effective; and 10% was off-label and not potentially clinically effective.[5] In Canada (except Quebec), Canadian Blood Services supplies IVIG to hospitals with no charge; however, there is no formal mechanism for oversight regarding IVIG use.[2,3,5] Each dose of IVIG can cost between $550 and $2200 CAD per child and between $2000 and $8000 CAD per adult; this does not include other associated costs of treatment.[1] From April 2005 to March 2006, this IVIG use cost Canadian Blood Services $196.1 million CAD.[3]

The purpose of this Rapid Response Report is to collect, critically appraise and evaluate the current evidence on the clinical effectiveness off-label use of intravenous immunoglobulin for the treatment of neurological or neuromuscular conditions. This report is a full-text review of studies originally identified in the CADTH Rapid Response Summary of Abstracts report: Off-Label Use of Intravenous Immunoglobulin for Neurological Conditions.[9]

Research Question

What is the clinical effectiveness of the off-label use of intravenous immunoglobulin for the treatment of neurological or neuromuscular conditions?

Key Findings

Sixteen systematic reviews (SRs; five with meta-analyses) and eight randomized controlled trials were identified regarding the clinical effectiveness of off-label use of intravenous immunoglobulin (IVIG) for the treatment of neurological or neuromuscular conditions.

There were mixed results regarding the impact of IVIG on epilepsy (from four SRs) and chronic inflammatory demyelinating polyneuropathy (from three SRs). In addition, there was insufficient evidence from three SRs to assess the effectiveness of IVIG in acute disseminated encephalomyelitis, and insufficient evidence from one SR to comment on the effectiveness of IVIG for the treatment of IgM anti-MAG paraprotein-associated demyelinating peripheral neuropathy.

IVIG was reported to be no better than placebo or plasma exchange for the treatment of myasthenia gravis in three SRs, while one SR concluded that IVIG may improve response in patients with myasthenia gravis. For patients with encephalitis, one meta-analysis showed no difference between IVIG and placebo for disability outcomes or adverse events, and three other SRs did not find sufficient evidence of an effect after treatment with IVIG to provide strong conclusions. IVIG was no better than placebo for Alzheimer's Disease, but was associated with fewer adverse events. IVIG was also no better than placebo for postpolio syndrome and reporting of adverse events was lacking. For patients with Rasmussen Syndrome, one SR did not identify sufficient data regarding IVIG use, and another SR found that IVIG was no better than tacrolimus for the treatment of this condition.

Evidence from three SRs suggested that IVIG may be better than plasma exchange for the treatment of pediatric Guillain-Barré Syndrome; however, one SR suggested that plasma exchange resulted in better outcomes than IVIG for children with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections. One SR suggested that some immunosuppressant agents (rituximab, mycofenolate) were better than IVIG for neuromyelitis optica, while others (mitoxantrone, cyclophosphamide, natalizumab) were better than IVIG in pediatric multiple sclerosis. However, IVIG was shown to be more effective than placebo for the treatment of multiple sclerosis in adults, while another SR found insufficient data comparing IVIG with placebo for the treatment of neuromyelitis optica to make a strong conclusion regarding its effectiveness.

While several studies concluded that off-label IVIG treatments of neurological or neuromuscular conditions may be promising compared with placebo or alternative treatments, many of the identified studies on were at high risk of bias due to rarity of disease (or outcome), small sample size (low power), open-label design, short follow-up, high involvement of industry, and lack of protocol registration. Therefore, results should be interpreted with caution. Additional high quality data from larger, long-term studies are required to make stronger conclusions.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and October 17, 2017. Internet links were provided, where available.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion in the CADTH Rapid Response Summary of Abstracts report: Off-Label Use of Intravenous Immunoglobulin for Neurological Conditions.[9] The final selection of full-text articles for inclusion in the current report was based on the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients any age with neurological or neuromuscular conditions that are not approved indications for intravenous immunoglobulin, including but not limited to: • Acute disseminated encephalomyelitis • Acute idiopathic dysautonomia • Bickerstaff encephalitis • Central nervous system vasculitis • Cerebral infarction with antiphospholipid antibodies • Chronic inflammatory demyelinating polyneuropathy • Chronic regional pain syndrome • Eaton-Lambert myasthenic syndrome • Myasthenia Gravis • Neuromyotonia • Paraproteinaemic demyelinating neuropathy • Relapsing-remitting multiple sclerosis • Stiff person syndrome
Intervention	Human intravenous immunoglobulin or subcutaneous immunoglobulin products, including but not limited to those available in Canada, alone or in combination with corticosteroids or other immunomodulation therapy.
Comparator	Treatment as usual, placebo, no treatment
Outcomes	Clinical benefits and harms
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012.

Critical Appraisal of Individual Studies

The included systematic reviews (SRs)[10-25] were critically appraised using AMSTAR II[26] and randomized controlled trials (RCTs)[27-34] were critically appraised using the Cochrane Risk of Bias tool for RCTs[35] and the external validity component of the Downs and Black checklist.[36] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 494 citations were identified in the literature search. Following screening of titles and abstracts, 462 citations were excluded and 32 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, nine publications were excluded for various reasons, while 24 publications met the inclusion criteria and were included in this report. These comprised 16 SRs and eight RCTs. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Myasthenia Gravis

Four SRs[13,17,23,24] (two with meta-analysis)[13,17] and two RCTs[31,33] were identified that included adult[13,17,31,33] and pediatric[23] patients with myasthenia gravis. One study compared IVIG with placebo;[13] five studies compared IVIG with plasma exchange;[13,17,23,31,33] one study compared IVIG with methylprednisolone;[13] and one study compared IVIG with corticosteroids.[23]

Two SRs evaluated symptoms with changes from baseline in Quantitative Myasthenia Gravis Score and changes in Manual Muscle Score;[13,17] one SR examined changes from baseline in Myasthenia Gravis Activities of Daily Living score;[13] one RCT evaluated changes from baseline of Myasthenia Gravis Quality of Life score;[31] another SR evaluated response to treatment;[23] one SR expressed efficacy, safety, and conditions of use for IVIG treatment of Myasthenia Gravis;[24] and another RCT measured duration of hospitalization stay, length of intensive care unit stay after surgery, length of intubation, duration of surgery, and dose of steroid administered.[33]

Guillain-Barré Syndrome

Three SRs[14,23,25] (one with meta-analysis)[14] were identified that included pediatric patients with Guillain-Barré Syndrome (GBS). All SRs compared IVIG with plasma exchange[14,23,25] or no treatment;[14,23,25] one SR compared IVIG with placebo;[14] two SRs compared IVIG with supportive therapy.[23,25]

The included SRs evaluated improvement in disability grade four weeks after randomization,[14] and time to improvement or recovery.[23,25]

Encephalitis

Four SRs[15,21,23,24] (one with meta-analysis)[15] were identified that included pediatric patients with encephalitis,[15,21] pediatric patients with N-methyl-D-aspartate receptor antibody encephalitis,[23] and autoimmune encephalitis.[24] Two SRs compared IVIG with no comparator;[21,23] another SR compared IVIG with placebo and with standard care;[15] one SR compared IVIG with corticosteroids, plasma exchange, and/or rituximab.[23]

Included SRs evaluated symptoms with disability measured by changes from baseline in the Liverpool Outcome Score;[15] greater than or equal to one adverse event;[15] length of hospital stay;[15] time until fever resolution;[15] clinical parameters;[21] recovery;[23] and expressed efficacy, safety, and conditions of use for IVIG treatment of encephalitis.[24]

Epilepsy

Four SRs[10,20-22] (two with meta-analysis)[10,20] were identified that included adult patients with refractory epilepsy[10,22], pediatric patients with drug-resistant epilepsy,[21] and pediatric patients with intractable epilepsy secondary to focal cortical dysplasia.[20] One SR compared IVIG and antiepileptic drugs with placebo and antiepileptic drugs;[10] another SR compared IVIG with antiepileptic drugs.[22]

Included SRs evaluated symptoms with 50% or greater reduction in seizure frequency;[10,20,21] adverse events;[10,22] global assessment;[10] clinical improvement;[21] as well as electrographic seizure control and patient outcome.[22]

Alzheimer's Disease

One SR[24] and three RCTs[27,30,32] were identified that included adult patients with Alzheimer's Disease.[24,27,30,32] The three RCTs all compared IVIG with placebo.[27,30,32]

The SR expressed efficacy, safety, and conditions of use for IVIG treatment of Alzheimer's Disease.[24] The RCTs evaluated the median area under the curve of plasma concentration of $A\beta_{1–40}$ between the last infusion and the final visit;[27] annualised per cent change in ventricular volume (APCV) as measured by MRI at baseline;[30] the change in the Cognitive subscale of the Alzheimer's Disease Assessment Scale from baseline;[27,30,32] change in the Clinical Dementia Rating-Sum of Boxes from baseline;[27,30] change in the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale from baseline;[27,32] change in Mini-Mental State Examination scores from baseline;[27,30] as well as change from baseline of Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change, Neuropsychiatric Inventory and Quality of Life in Alzheimer's Disease Scale.[32]

Postpolio Syndrome

Two SRs with meta-analysis were identified that included adult patients with Postpolio syndrome.[11,16] They both compared IVIG with placebo.[11,16]

One SR evaluated activity limitations with the Short Form-36 Health Survey Physical Component Summary as well as adverse events,[11] while the other SR measured pain severity, fatigue scores, and muscle strength.[16]

Acute Disseminated Encephalomyelitis

Four SRs[12,23-25] (one with meta-analysis)[12] were identified that included adults with demyelinating peripheral neuropathy,[12] as well as pediatric[23] and adult[25] patients with acute

disseminated encephalomyelitis. One SR compared IVIG with placebo or Interferon alfa-2a;[12] two SRs compared IVIG with plasma exchange;[23,25] one SR compared IVIG with corticosteroids or supportive care;[23] and one SR compared IVIG with methylprednisolone.[25]

Included SRs evaluated symptoms using change in Clinical Neuropathy Disability Score from baseline;[12] change in subjective score from baseline;[12] number of patients improved by at least 20% on neuropathy impairment scale from baseline ;[12] recovery rates;[23] relapse rates;[23] as well as expressed efficacy, safety, and conditions of use for IVIG treatment of Acute Disseminated Encephalomyelitis.[24]

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections

Two SRs were identified that included pediatric patients with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).[24,25] One SR compared IVIG with placebo or plasma exchange.[25] One SR evaluated the efficacy, safety, and conditions of use for IVIG treatment of PANDAS.[24]

Neuromyelitis Optica

Two SRs[24,25] and one RCT[29] were identified that included patients with neuromyelitis optica,[24,25] adult patients and pediatric patients with transverse myelitis and neuromyelitis optica.[29] One SR compared IVIG with rituximab or mycofenolate mofetil or methylprednisolone or azathioprine.[25] The RCT compared IVIG and intravenous methylprednisolone with intravenous methylprednisolone alone.[29]

One SR evaluated the efficacy, safety, and conditions of use for IVIG treatment of neuromyelitis optica.[24] The RCT examined the change in American Spinal Injury Association Impairment Scale score from baseline, the change in Expanded Disability Status Scale score from baseline, and the change in EuroQol-5 Dimensions youth version score from baseline.[29]

Rasmussen Syndrome

Two SRs were identified that included patients with Rasmussen Syndrome.[23,24] One SR compared IVIG with tacrolimus.[23] Symptoms were evaluated using seizure frequency;[23] as well as the efficacy, safety, and conditions of use for IVIG treatment of Rasmussen Syndrome.[24]

Multiple Sclerosis

Three SRs[19,24,25] (one with meta-analysis)[19] were identified that included patients with remitting multiple sclerosis[19] or multiple sclerosis.[24,25] One SR compared IVIG with placebo,[19] while another compared IVIG with mitoxantrone or cyclophosphamide or natalizumab or IFN-band steroid.[25]

One SR evaluated symptoms using the the change in Expanded Disability Status Scale score from baseline;[19] while another measured the efficacy, safety, and conditions of use for IVIG treatment of multiple sclerosis.[24]

Chronic Inflammatory Demyelinating Polyneuropathy

Three SRs[18,23,24] (one with meta-analysis)[18] were identified that included adult[18] and pediatric[23] patients with chronic inflammatory demyelinating polyneuropathy. One SR

compared subcutaneous immunoglobulin with IVIG,[18] while another compared IVIG with plasma exchange or corticosteroids.[23]

Symptoms were evaluated using the change in Medical Research Council Sum Score from baseline and adverse events[18] as well as measured the efficacy, safety, and conditions of use for IVIG treatment of chronic inflammatory demyelinating polyneuropathy.[24]

IgM Anti-MAG Paraprotein-Associated Demyelinating Peripheral Neuropathy

One SR with meta-analysis were identified that included patients with IgM anti-MAG paraprotein-associated demyelinating peripheral neuropathy comparing IVIG with placebo or no treatment.[12]

Symptoms were evaluated using the change in Clinical Neuropathy Disability Score (CNDS) between baseline and six months, subjective score at six months, and number of participants improved by at least 20% on Neuropathy Impairment Scale (NSI) at 6 months.

Summary of Critical Appraisal

Systematic Reviews and Meta-Analyses

All the SRs[10-25] included in this review stated clear research questions and inclusion criteria, and three SRs[16,17,21] also included timeframe for follow-up as part of their inclusion criteria. Five SRs[10-14] were updates of previously published SRs, one SR's[16] protocol was registered with PROSPERO, and one SR[24] established review questions, search strategy, and inclusion plus exclusion criteria prior to conduct of review, but no other SRs[15,17,23,25] mentioned that a protocol preceded review conduct, which could potentially lead to selective outcome reporting. All SRs[10-19,21-25] except one[20] explained their inclusion of RCTs, five SRs[11-14,16] of quasi-RCTs, seven SRs[10,17,18,21-23,25] of non-randomized studies of interventions (NRSIs), and one SR[20] did not discuss study design inclusion.

Fourteen SRs[10-20,22,24,25] searched at least two databases, provided word and/or search strategy, and justified publication restrictions. Fifteen SRs[10-20,22-25] searched reference lists of included studies. Thirteen SRs[10-20,22,24] searched for grey literature. Eleven SRs[10-17,19,22,24] searched trial/study registries, consulted experts, conducted search within 24 months of completion of review. It is unclear for two SRs[21,23] if their literature search was sufficiently comprehensive.

Study selection for inclusion and data extraction was performed in duplicate for ten SRs,[10-15,17,21,23,24] only study selection was performed in duplicate in three SRs,[17,22,25] only data extraction was performed in duplicate in two SRs,[16,18] and two SRs[19,20] did not perform study selection or data extraction in duplicate which could potentially lead to selection bias. Six SRs[10-15] provided a list of all potentially relevant studies that were read in full-text review but were excluded and justified each exclusion while the ten other SRs[16-25] did not justify exclusion from the review.

All sixteen SRs[10-25] described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail but only one SR[12] reported sources of funding for each included study. Nine SRs[10-16,19,21] assessed the risk of bias (ROB) in individual studies that were included in the review using the Cochrane Handbook for Systematic Reviews of Interventions ROB method. Other methods of bias assessment included the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool,[10-15,22] the

Oxford Centre for Evidence-Based Medicine criteria for levels of evidence,[17,22,23] the Newcastle-Ottawa Scale (NOS),[18] and the Jadad checklist.[19] However, three SRs[20,24,25] did not assess ROB in their included studies or discuss its impact on the results and interpretation of the meta-analysis (MA), which could lead to a biased conclusion and so their results should be interpreted with caution. Nine SRs[10-18] discussed ROB impact on the results and interpretation of the MA, while one SR[19] conducted a ROB assessment, but did not discuss the ROB impact on the results and interpretation of the MA. Five SRs[10,11,15,17,18] discussed the likelihood and impact of publication bias but only three SRs[11,17,18] performed graphical tests and statistical tests for it – the other six systematic reviews with meta-analysis[12-14,16,19,20] did not discuss risk of publication bias in their results and so their conclusions could have been affected by publication bias.

Eleven SRs[10-20] justified combining the data in a MA, with ten SRs[10-19] using an appropriate weighted technique and adjusting for heterogeneity. Four SRs[10,12-14] found no heterogeneity and six SRs[11,15-19] investigated potential sources of heterogeneity. Nine SRs[11,12,15-18,21-23] discussed the impact of heterogeneity on their results while four SRs[19,20,24,25] did not. Thirteen SRs[10-17,20-22,24,25] reported no competing interests with ten SRs[10-16,21,23,24] describing their sources of funding. Two SRs[18,19] did not address competing interests or funding and one SR[23] did not address how its competing interests were managed. Additional bias can be introduced into the results and conclusions of a review though competing interests.

Randomized Controlled Trials

All the RCTs[27-34] included in this review are at definitely low risk of selection bias due to sequence generation because they all described a random component in the sequence generation process and six RCTs[27-31,34] described a method of allocation concealment such that participants and investigators enrolling participants could not foresee assignments, although two RCTs[32,33] provided insufficient information to permit judgement. Three RCTs[27,29,30] are at definitely low risk of performance bias and detection bias because all relevant people were blinded or their non-blinding would not likely bias the results. Three RCTs[28,31,32] are at probably low risk of performance or detection bias because blinding was not described in detail and two RCTs[33,34] are at definitely high risk of bias because no one was blinded and their non-blinding would likely bias the results.

Seven RCTs[27-29,31-34] are at definitely low risk of attrition bias due to incomplete outcome data because of either no missing data,[29,31,33] missing data balanced across groups,[27,28,34] or multiple imputation filled in missing outcome data.[32] One RCT[30] provided insufficient information to permit judgement. Three RCTs[27,29,32] are at definitely low risk of reporting bias due to selective outcome reporting because the study protocol is available and all of the study's outcomes have been reported as specified. Five RCTs[28,30,31,33,34] are at probably high risk because two were long-term follow-ups to registered trials but had long-term outcomes that were not originally registered,[28,31] redefined a primary outcome[30] or provided insufficient information.[33,34] Six RCTs[27,29-32,34] are at risk of bias due to industry involvement.

In eight RCTs[27-34] external validity was not clear as the description of whether subjects asked to participate in the study were representative of the entire population from which they were recruited was lacking. Seven RCTs[27,28,30-34] described subjects who were prepared to participate who were representative of the entire population from which they were recruited, one RCT[29] described a very selective population which could not be generalized to the entire population of interest. Three RCTs[27,33,34] described staff, places, and facilities where the patients were treated which were representative of the treatment

the majority of patients receive whereas three other RCTs[28-30] described staff, places, and facilities where the patients were treated which were not representative of the treatment the majority of patients receive or generalizable to the target population, and two RCTs[31,32] did not describe staff, places, and facilities where the patients were treated.

Summary of Findings

Detailed findings of the individual studies are provided in Appendix 4.

What is the clinical effectiveness of the off-label use of intravenous immunoglobulin for the treatment of neurological or neuromuscular conditions?

Myasthenia Gravis

Four SRs[13,17,23,24] (two with meta-analysis)[13,17] and two RCTs[31,33] studied the impact of IVIG on myasthenia gravis.

Functional Outcomes

IVIG was no better than placebo at 14-day, 28-day, or 42-day follow-up in mean change of Quantitative Myasthenia Gravis Score (QMGS) from baseline.[13] IVIG was slightly better than placebo at 42-day follow-up in the Myasthenia Gravis Activities of Daily Living (MG-ADL) score.[13] IVIG was suggested to be a possible treatment option for myasthenia gravis exacerbation or crisis, but there were insufficient data for treatment of the chronic form of myasthenia gravis when compared with placebo or no intervention.[24]

IVIG was no better than plasma exchange at 14-day or 28-day follow-up but was slightly better at 21-day follow-up for mean change in QMGS from baseline.[13] IVIG was no better than plasma exchange at 15-day follow-up for mean change in Myasthenic Muscular Score (MMS) from baseline.[13] IVIG was no better than plasma exchange for clinical efficacy (changes in the MMS or QMGS between 1- and 15-day follow-up after treatment or randomization) odds ratio 0.561 (0.224 to 1.408, $P = 0.218$).[17]

IVIG was no better than methylprednisolone at 14-day follow-up for mean change in QMGS from baseline.[13]

IVIG lead to a good response (no or minimal functional impairment or limitation of activities) to initial treatment in 78% of patients (n=59).[23]

Quality of Life

One RCT[31] reported quality of life outcomes for IVIG compared with placebo. The trial reported no statistical difference in the change on myasthenia gravis quality of life 60-item (MG-QOL-60) or 15-item (MG-QOL-15) scores at two weeks post-treatment ($P = 0.52$ and 0.41, respectively).

Hospital Metrics

One RCT[33] comparing IVIG to plasma exchange reported no significant difference in duration of hospital stay (20.27 ± 8.42 days versus 21.08 ± 5.29 days, $P = 0.78$) or length of ICU stay after surgery (2.33 ± 1.49 days versus 3.75 ± 3.10 days, $P = 0.16$). However the same trial[33] reported that the duration of surgery was shorter in the IVIG group (3.46 ± 0.68 hours) compared with plasma exchange (4.17 ± 1.03 hours; $P = 0.05$). There was no statistically significant difference between groups in the dose of steroid administered.[33]

Adverse Events

A SR found that IVIG was no better than plasma exchange for adverse events (odds ratio 0.654 [0.166 to 2.572], *P* = 0.543).[17]

Pediatric Guillain-Barré Syndrome (GBS)

Three SRs[14,23,25] (one with meta-analysis)[14] studied the impact of IVIG on Guillain-Barré Syndrome in pediatric patients.

Functional Outcomes

IVIG reduced time to return of function, but not improvement of maximum disability score.[23] Plasma exchange was better than IVIG for ventilated patients with GBS.[23]

IVIG was better than supportive treatment alone for change in disability grade four weeks after randomization, mean difference 1.42 (2.57 to 0.27).[14] One SR identified five small primary studies on children with GBS (n ≤ 51 for each study) treated with IVIG which showed mixed results; however, this review concluded that IVIG was a possible treatment option for pediatric GBS when compared with supportive care or plasma exchange.[25]

Encephalitis

Four SRs[15,21,23,24] (one with meta-analysis)[15] studied the impact of IVIG on encephalitis.

Functional Outcomes

One meta-analysis showed that there was no statistical difference between IVIG and placebo for disability at three to six months, risk ratio 0.75 (0.22 to 2.60, *P* = 0.65) and significant disability at discharge, risk ratio 1.00 (0.60 to 1.67, *P* = 1.0).[15] Another SR reported that no significant improvements were found in children with encephalitis treated with IVIG (post-treatment or when compared with a tacrolimus-treated group).[21] A third SR suggested that IVIG possibly improves recovery in N-methyl-D-aspartate receptor antibody encephalitis.[23] The fourth SR concluded that there were insufficient data regarding treatment of autoimmune encephalitis when compared with placebo or no intervention.[24]

Adverse Events

One SR showed that IVIG was no better than placebo for risk of: greater than or equal to one serious adverse event, risk ratio 1.00 (0.07 to 14.05, *P* = 1.0); mortality, risk ratio 0.50 (0.05 to 4.75, *P* = 0.55); hypotension, risk ratio 1.00 (0.07 to 14.05, *P* = 1.0); or melaena, risk ratio 1.00 (0.07 to 14.05, *P* = 1.0).[15]

Epilepsy

Four SRs[10,20-22] (two with meta-analysis)[10,20] studied the impact of IVIG on epilepsy.

Seizure Frequency and Severity

IVIG was no better than placebo for ≥ 50% reduction in seizure severity in patients with refractory epilepsy, risk ratio 1.76 (0.79 to 3.93, *P* = 0.17) and in patients with refractory partial epilepsy, risk ratio 3.08 (0.84 to 11.34, *P* = 0.091).[10] From one SR, IVIG reduced seizure frequency by greater than 50% in six out of eight pediatric patients (*P* < 0.05).[20] Another SR reported mixed results in terms of reduction of seizure frequency (clinical improvement) for pediatric patients as well as a lack of clear definitions for reduction of

seizure frequency and clinical improvement.[21] In the fourth SR, seizure reduction and/or control occurred in 15 of 33 adult patients (1 partial response and 14 complete responses) for refractory status epilepticus.[22]

Adverse Events

No adverse events were reported in two SRs,[10,22] and no serious adverse events were reported in two other reviews.[20,21] Two mild adverse events (post-infusion paresthesia and transient increase in temperature) were reported for pediatric epilepsy.[20]

Global Assessment

In terms of Global Assessment (integration of several clinical aspects including reduction in the number and severity of seizures, evolution of EEG, interictal status, and perception of the participants and caregivers), IVIG was better than placebo; risk ratio 3.21 (1.10 to 9.36, *P* = 0.033) for refractory epilepsy.[10]

Alzheimer's Disease

One SR[24] and three RCTs[27,30,32] studied the impact of IVIG on Alzheimer's Disease.

Functional Outcomes

IVIG was reported to be no better than placebo for: annualised per cent change in ventricular volume (APCV) as measured by MRI at baseline, 12 and 24 months following the first infusion;[30] change in cognitive performance between baseline, 12 and 24 months after the first infusion as measured by Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog);[30,32] change in cognitive performance between baseline, 12 and 24 months after the first infusion as measured by Mini Mental State Examination (MMSE);[30] cognitive performance between baseline, 12 and 24 months after the first infusion as measured by CDR-Sum of Boxes (CDR-SB); [30] and change in Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL) between baseline, 9 months, and 18 months.[32]

One SR concluded that IVIG is a not possible treatment for Alzheimer's Disease (due to inadequate efficacy, a lack of pathophysiological justification or potentially harmful effect) when compared with placebo or no intervention.[24]

Adverse Events

One RCT reported that serious and non-serious adverse events were higher in the placebo group than the IVIG group.[27]

Postpolio Syndrome

Two SRs with meta-analysis[11,16] studied the impact of IVIG on postpolio syndrome.

Activity Limitations

One meta-analysis showed that IVIG was no better than placebo for improvement in activity limitations as measured by the Short Form-36 Health Survey Physical Component Summary (SF-36 PCS) for either short term (< 3 months) mean difference 2.35 (-0.06 to 4.76, *P* = 0.056); or long term (> 3 months) mean difference -0.51 (-4.63 to 3.60, *P* = 0.81).[11]

Pain

Both SRs found that IVIG was no better than placebo for pain as measured by Visual Analogue Scales (VASs) weighted mean difference -1.02 (-2.51 to 0.47)[16] including short term, mean difference -9.27 (-25.11 to 6.57, *P* = 0.25);[11] and long term, mean difference -5.61 (-14.95 to 3.73, *P* = 0.24).[11]

In addition, IVIG was no better than placebo for pain as measured by Pain Drawing Instrument (PDI) or 101-point numeric rating scale for pain (101NRS) for either: short term, mean difference on PDI of -6.70 (-23.63 to 10.23, *P* = 0.44) and mean difference on 101NRS of -3.00 (-16.30 to 10.30, *P* = 0.66); or long term, mean difference on PDI of -5.50 (-23.39 to 12.39, *P* = 0.55) and mean difference on 101NRS of 0.0 (-13.03 to 13.03, *P* = 1.0).[11]

Fatigue

There was no statistical difference between IVIG and placebo for fatigue as measured by the Fatigue Severity Scale (FSS) or the Multidimensional Fatigue Index (MFI), weighted mean difference 0.28 (-0.56 to 1.12).[16] IVIG was no better than placebo in FSS for the short term, mean difference 0.08 (-0.71 to 0.87, *P* = 0.85), or the long term, mean difference -0.50 (-1.15 to 0.15, *P* = 0.13).[11] IVIG was no better than placebo in MFI in the short term, mean difference 0.0 (-1.05 to 1.05, *P* = 1.0).[11]

Muscle Strength

IVIG was no better than placebo for muscle strength as measured by the Muscle Strength Medical Research Council (MRC) grading scale and a dynamometer, mean difference 1.68 (0.03 to 3.32, *P* = 0.05).[16] There was no statistical difference between IVIG and placebo for muscle strength post-treatment isometric strength right knee extensor for either the short term, mean difference -11.01 (-53.86 to 31.84, *P* = 0.61), or the long term, mean difference -10.29 (-55.37 to 34.78, *P* = 0.65).[11] However, IVIG was favoured over placebo for percent change in isometric strength of polio effected muscle in the short term, mean difference 8.60 (2.81 to 14.39, *P* = 0.0036) .[11]

Adverse Events

There was insufficient reporting of adverse events in one SR.[11]

Acute Disseminated Encephalomyelitis (ADEM)

Three SRs[23-25] studied the impact of IVIG on ADEM.

Functional Outcomes

The SRs concluded that IVIG is a possible treatment option for ADEM when compared with placebo[24] or no intervention.[23,24] IVIG and corticosteroids were also suggested to be a possible treatment option for ADEM.[23] One SR concluded that IVIG is a possible treatment option for pediatric ADEM in steroid-resistant cases, though these conclusions were based on case reports and case series.[25]

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS)

Two SRs[24,25] studied the impact of IVIG on PANDAS.

Functional Outcomes

One SR reported that, based on one included RCT, more patients treated with plasma exchange than IVIG showed improvement in obsessive compulsive disorder scores, depression, anxiety, tics and global function; however, between-group statistical comparisons were not reported.[25] Another SR concluded that there is insufficient data regarding the treatment of PANDAS when compared with placebo or no intervention.[24]

Neuromyelitis Optica

Two SRs[24,25] and one RCT[29] studied the impact of IVIG on neuromyelitis optica.

Functional Outcomes

Immunosuppressant agents (rituximab, mycofenolate) were better than IVIG for the treatment of children with neuromyelitis opica in a few small studies or case reports (n < 5) identified by one SR.[25] Both SRs concluded that there is insufficient data for treatment of neuromyelitis optica with IVIG when compared with placebo or no intervention.[24,25] The RCT was ended early due to low recruitment and was unable to provide results.[29]

Rasmussen Syndrome

Two SRs[23,24] studied the impact of IVIG on Rasmussen Syndrome.

Functional Outcomes

One SR showed that IVIG was no better than tacrolimus in reduction or stopping of seizures,[23] while another SR concluded that while there were insufficient data identified regarding IVIG use in Rasmussen Syndrome, it may still be considered as a possible treatment option when compared with placebo or no intervention.[24]

Multiple Sclerosis

Three SRs[19,24,25] (one with meta-analysis)[19] studied the impact of IVIG on Multiple Sclerosis.

Functional Outcomes

IVIG was slightly better than placebo for the proportion of patients: remaining relapse-free at the end of the treatment period, mean difference 1.69 (1.205 to 2.380); improved in Expanded Disability Status Scale (EDSS), odds ratio 2.977 (1.769 to 5.010, *P* = 0.0001); deteriorated in EDSS, odds ratio 0.522 (0.330 to 0.827, *P* = 0.006) for relapsing-remitting Multiple Sclerosis.[19] IVIG was better than placebo for reduction in annualized relapse rate (number of relapses per annum in each treatment arm), standardized mean difference -0.218 (-0.412 to -0.024, *P* = 0.028), but not better than placebo for change in EDSS from baseline, standardized mean difference -0.025 (-0.211 to 0.161, *P* = 0.860) for relapsing-remitting Multiple Sclerosis.[19]

Immunosuppressant agents (mitoxantrone, cyclophosphamide, natalizumab) were reported to be better than IVIG in one SR evaluating patients with pediatric multiple sclerosis, and the authors commented that IVIG is not recommended for routine treatment of this population.[25]

Two other SRs also concluded that IVIG is a possible alternative therapy, or second-line treatment option for remitting multiple sclerosis, when compared with placebo[19,24] or no

intervention,[24] but not for primary- or secondary-progressive multiple sclerosis (due to inadequate efficacy, a lack of pathophysiological justification or potentially harmful effect) when compared with placebo or no intervention.[24]

Chronic Inflammatory Demyelinating Polyneuropathy

Three SRs[18,23,24] (one with meta-analysis)[18] studied the impact of IVIG on chronic inflammatory demyelinating polyneuropathy.

Functional Outcomes

There was no statistically significant difference between SCIG and IVIG on the Medical Research Council Sum Score (MRC-SS) for muscle strength, mean difference 0.84 (-0.01 to 1.69).[18]

The other two SRs concluded that IVIG is a possible first-line treatment option for chronic inflammatory demyelinating polyneuropathy, when compared with placebo,[24] no intervention,[24] corticosteroids,[23] or plasma exchange.[23]

IgM Anti-MAG Paraprotein-Associated Demyelinating Peripheral Neuropathy

One SR with meta-analysis studied the impact of IVIG on IgM anti-MAG paraprotein-associated demyelinating peripheral neuropathy.[12]

Functional Outcomes

No data were available at six months for change in Clinical Neuropathy Disability Score (CNDS) between baseline and six months, subjective score at six months, or number of participants improved by at least 20% on the Neuropathy Impairment Scale (NSI) at 6 months for patients with IgM anti-MAG paraprotein-associated demyelinating peripheral neuropathy.[12] The SR concluded that there were insufficient data for treatment of IgM anti-MAG paraprotein-associated demyelinating peripheral neuropathy with IVIG when compared with placebo or no intervention.[12]

Limitations

There were a number of limitations within the evidence of off-label IVIG use for neurological or neuromuscular conditions. For all of the conditions examined here, there were many different outcomes between studies such that meta-analysis was often unrealistic. The outcomes themselves either had short follow-ups, or did not mention how long the follow-up was, which led to insufficient collection of data, particularly when paired with rare diseases and outcomes.

The lack of protocol registration and open-label designs included in many SRs could have introduced selection bias. In the meta-analyses, publication bias was rarely assessed or even discussed and risk of bias in general was rarely tied to the results and conclusions of the studies. Conflicts of interest arising from study funding was also an issue. The SRs were lacking in descriptions of duplicate study selection as well as data extraction. The included RCTs were lacking in external validity. As such, the results of this report must be interpreted with caution.

Conclusions and Implications for Decision or Policy Making

There were mixed results regarding the impact of IVIG on epilepsy and chronic inflammatory demyelinating polyneuropathy, from four SRs[10,20-22] and three SRs,[18,23,24] respectively. In addition, there was insufficient evidence from three SRs[23-25] to assess the effectiveness of IVIG in ADEM, and insufficient evidence from one SR[12] to comment on the effectiveness of IVIG for the treatment of IgM anti-MAG paraprotein-associated demyelinating peripheral neuropathy. It is therefore unclear as to whether this off-label use of IVIG is actually effective, and higher quality evidence is required to determine the impact of IVIG on these four conditions.

IVIG was reported to be no better than placebo or plasma exchange for the treatment of myasthenia gravis in three SRs,[13,17,24] while one SR concluded that IVIG may improve response in patients with myasthenia gravis.[23] For patients with encephalitis, one meta-analysis showed no difference between IVIG and placebo for disability outcomes or adverse events,[15] and three other SRs did not find sufficient evidence of an effect after treatment with IVIG to provide strong conclusions.[21,23,24] Data from one SR[24] and three RCTs[27,30,32] suggested that IVIG was no better than placebo for the management of Alzheimer's Disease, but was associated with fewer adverse events. Two SRs[11,16] reported that IVIG was no better than placebo for postpolio syndrome and reporting of adverse events associated with treatment was lacking. For patients with Rasmussen Syndrome, one SR[24] did not identify sufficient data regarding IVIG use, and another SR[23] found that IVIG was no better than tacrolimus for the treatment of this condition. Off-label use of IVIG in myasthenia gravis, encephalitis, Alzheimer's Disease, postpolio syndrome, and Rasmussen Syndrome appears to be no more effective than their respective comparators (which in many cases was placebo); higher quality evidence is required to determine the impact of IVIG on these conditions.

Evidence from three SRs[14,23,25] suggested that IVIG may be better than plasma exchange for the treatment of pediatric Guillain-Barré Syndrome; however, one SR[25] suggested that plasma exchange resulted in better outcomes than IVIG for children with PANDAS. More, higher quality evidence is required to determine the comparative effectiveness of IVIG versus plasma exchange for children with PANDAS and Guillain-Barré Syndrome.

One SR[25] suggested that the immunosuppressant agents rituximab and mycofenolate were better than IVIG for neuromyelitis optica and that mitoxantrone, cyclophosphamide, and natalizumab were better than IVIG for the treatment of pediatric multiple sclerosis. However, IVIG was shown to be more effective than placebo for the treatment of multiple sclerosis in adults,[19] while another SR found insufficient data comparing IVIG with placebo for the treatment of neuromyelitis optica to make a strong conclusion regarding its effectiveness.[24] Off-label use of IVIG appears to be less effective in neuromyelitis optica and pediatric multiple sclerosis than immunosuppressive agents; however, higher quality evidence is required to determine the impact of IVIG on these conditions.

While several studies concluded that off-label IVIG treatments of neurological or neuromuscular conditions may be promising compared with placebo or alternative treatments, many of the identified studies on were at high risk of bias due to rarity of disease (or outcome), small sample size (low power), open-label design, short follow-up, high involvement of industry, and lack of protocol registration. Therefore, results should be interpreted with caution. Additional high quality data from larger, long-term studies are required to make stronger conclusions.

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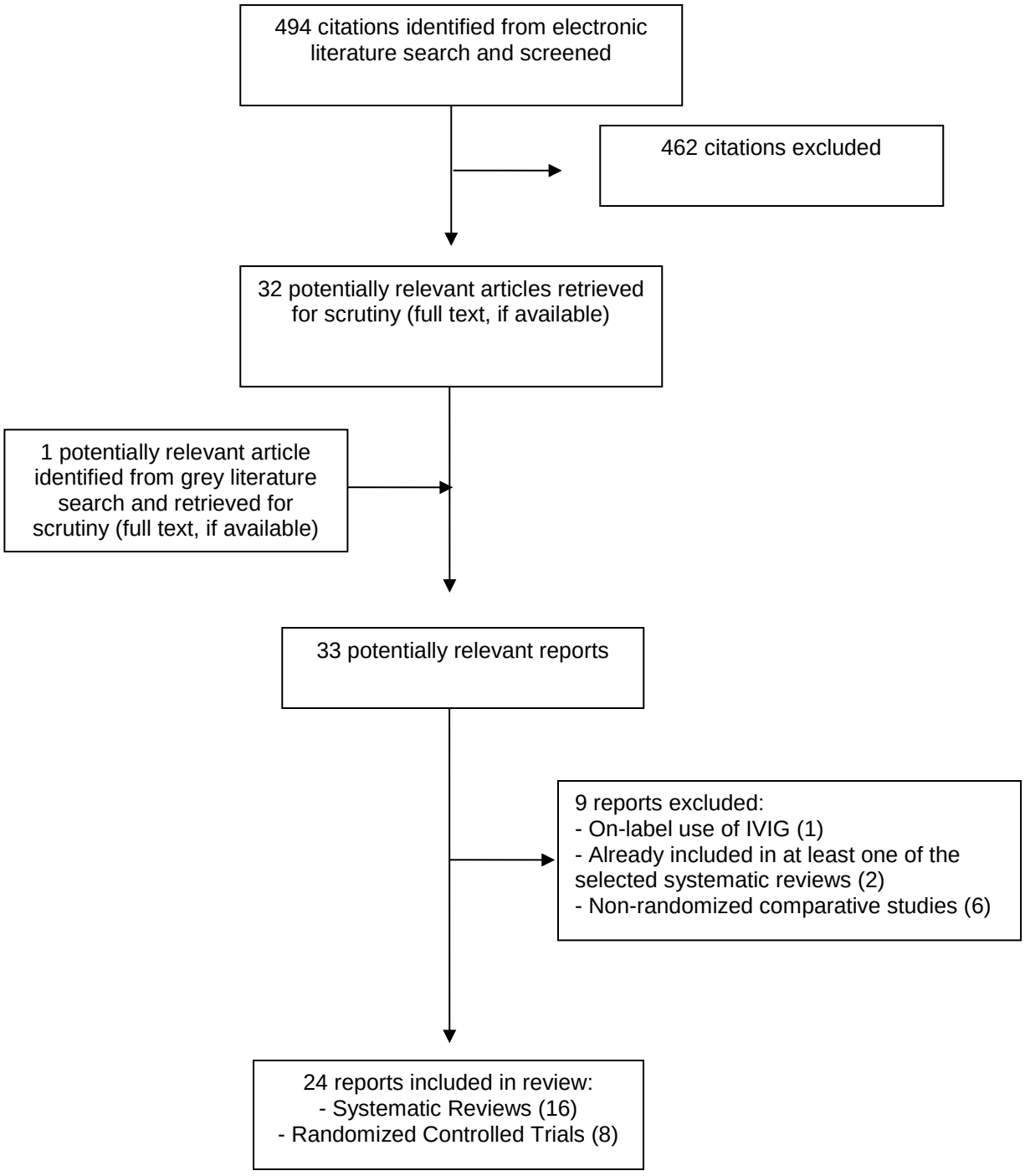
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews with Meta-Analyses

Author, Publication Date, Country	Study Design	Population[a]	Intervention	Comparator(s)	Outcomes
Geng, 2017[10] China	SR/MA	1 included randomized, add-on, double-blind, placebo-controlled, multi-centre trial 61 adult patients with refractory epilepsy	Regular antiepileptic drugs PLUS 100 IVIG per kilograms bodyweight, 250 grams IVIG per kilograms bodyweight, or 400 grams IVIG per kilograms bodyweight for 6 weeks	Regular antiepileptic drugs PLUS Placebo (2% human albumin solution) for 6 weeks	• 50% or greater reduction in seizure frequency • Incidence or severity of adverse effects • Global assessment
Koopman, 2015[11] The Netherlands, Norway	SR/MA	3 Double-blind, placebo-controlled RCTs 212 adult patients with PPS	IVIG	Placebo	• (Change in) Activity limitations ≤3 months – Measured with the SF-36 PCS1 (scale from 0 to 100) • Activity limitations > 3 months –Measured with the SF-36 PCS1 (scale from high disability at 0 to no disability at100) • Adverse events
Lunn, 2016[12] The United Kingdom, Italy	SR/MA	4 trials (2 included placebo-controlled cross-over design trials, 1 open-label design, 1 placebo-controlled double-blind design) 77 adults with a stable	IVIG	Placebo OR Interferon alfa-2a	• CNDS at six months • Subjective score at six months • Number of participants improved by at least 20% on NIS at 6 months

Author, Publication Date, Country	Study Design	Population[a]	Intervention	Comparator(s)	Outcomes
		or worsening demyelinating peripheral neuropathy			
Gajdos, 2012[13] France, Germany	SR/MA	7 included RCTs Adult patients with MG	IVIG	Placebo	• Change in QMGS day 0 to 14 • Change in QMGS day 0 to 28 • Change in QMGS day 0 to day 42 • Change in MG-ADL day 0 to 42
				PLEX	• Change in MMS day 0 to 15 • Change in QMGS day 0 to day 14 • Change in QMGS day 0 to day 21 • Change in QMGS day 0 to day 28
				Methylprednisolone	• Change in QMGS day 0 to 14
Hughes, 2014[14] The United Kingdom, The Netherlands	SR/MA	12 included trials 623 adult and pediatric patients with GBS in adult and pediatric populations	IVIG **off-label use in pediatric population	No treatment OR Placebo OR PLEX	Primary • Improvement in disability grade four weeks after randomisation Secondary • Time from randomisation until recovery of unaided walking • Time from randomisation until recovery of walking with aid • Time from randomisation until discontinuation of ventilation • Mortality • Death or disability (inability to walk without aid after 12 months) • Treatment-related fluctuation during the 12 weeks after randomisation, or a relapse • Adverse events,
Iro, 2017[15] The United Kingdom, New	SR/MA	3 included RCTs 139 pediatric patients with encephalitis	IVIG	Standard care OR Placebo	Primary: • Significant disability assessed using Liverpool Outcome Score with a follow-up of 3 to 6 months • ≥ 1 serious adverse event

Author, Publication Date, Country	Study Design	Population[a]	Intervention	Comparator(s)	Outcomes
Zealand					Secondary: • Significant disability at discharge • Length of hospital stay • Time to fever resolution • Time to stop spasms • Time to regain consciousness • Time to resolution of neuropathic symptoms
Huang, 2015[16] Taiwan	SR/MA	8 included studies (3 RCTs, 5 prospective studies) 508 adults with PPS	IVIG	Placebo (saline or glucose water)	• Pain severity • Fatigue scores • Muscle strength
Ortiz-Salas, 2016[17] Columbia	SR/MA	10 included studies 2112 adult patients with MG (aged 18 to 84 years)	IVIG	PLEX	• Change in MMS, or QMGS between day 1 and 15 days after the treatment began or the randomization was done
Racosta, 2017[18] Canada	SR/MA	6 included studies 88 patients with MMN 4 included studies 50 patients with CIDP	SCIG (Not approved for MMN or CIDP)	IVIG (Approved for MMN and CIDP)	Primary: • MRC-SS for muscle strength Secondary: • Risk of drug-related systemic and/or moderate adverse effects • Severity of adverse effects
Olyaeemanesh, 2016[19] Iran	SR/MA	6 included double-blinded RCTs 537 adult patients with RRMS	IVIG	Placebo	• Progression of the disease using the EDSS
Al Amrani, 2017[20]	SR/MA	4 included studies 8 pediatric patients	IVIG	No comparator	• Reduction of seizure frequency by more than 50% in the absence of any concomitant increase of dose - or introduction - of antiepileptic medication

Author, Publication Date, Country	Study Design	Population[a]	Intervention	Comparator(s)	Outcomes
Canada		with intractable epilepsy secondary to FCD (aged 0 to 18 years)			

CIDP = Chronic Inflammatory Demyelinating Polyneuropathy, CNDS = Clinical Neuropathy Disability Score, EDSS = Expanded Disability Status Scale, FCD = Focal Cortical Dysplasia, GBS = Guillain-Barré Syndrome, IVIG = Intravenous Immunoglobulin, MG = Myasthenia Gravis, MG-ADL = Myasthenia Gravis Activities of Daily Living, MMN = Multifocal Motor Neuropathy, MMS = Myasthenic Muscular Score, MRC-SS = Medical Research Council Sum Score, NIS = Neuropathy Impairment Scale, PLEX = Plasma Exchange, PPS = Postpolio Syndrome, QMGS = Quantitative Myasthenia Gravis Score, RCT = Randomized Controlled Trial, RRMS = Relapsing-Remitting Multiple Sclerosis, SCIG = Subcutaneous Immunoglobulin, SF-36 PCS1 = Short Form-36 Health Survey Physical Component Summary, SR/MA = Systematic Review with Meta-Analysis.

[a] Number of included studies represents the studies in the systematic review with relevant comparisons for this report.

Table 3: Characteristics of Included Systematic Reviews without Meta-Analyses

Author, Publication Date, Country	Study Design	Population[a]	Intervention	Comparator(s)	Outcomes
Gogou, 2017[21] Greece	SR	9 included prospective studies 131 pediatric patients with drug-resistant epilepsy	IVIG	None	• >50% decrease in seizure frequency • Clinical improvement
		2 included prospective studies 38 pediatric patients with encephalitis			• Clinical parameters
Zeiler, 2017[22] Canada	SR	24 included studies 33 adult patients with refractory status epilepticus (aged 18 to 69)	IVIG	Anti-epileptic drugs	Primary: • Electrographic seizure control Secondary: • Patient outcome • Adverse events
Gadian, 2017[23] The United Kingdom	SR	13 included studies (2 RCTs, 2 cohort studies, and 9 series) 316 pediatric patients with GBS	IVIG	No treatment OR PLEX OR Supportive care OR Historical controls	• Time to improvement
		10 series 114 pediatric patients with CIDP		Corticosteroids OR PLEX OR None	• Response to initial treatment
		10 included studies 67 pediatric patients with		Corticosteroids OR PLEX	• Response to treatment

Author, Publication Date, Country	Study Design	Population[a]	Intervention	Comparator(s)	Outcomes
		generalized and ocular MG		OR None	
		7 included series 30 pediatric patients with ADEM		Corticosteroids OR PLEX OR Supportive care OR None	• Recovery rates • Relapse rates
		2 included series 6 pediatric patients with N-methyl-D-aspartate receptor antibody encephalitis		Corticosteroids, PLEX, AND/OR Rituximab OR None	• Recovery
		6 included studies (5 series and 1 RCT) 34 patients with RS		Tacrolimus OR None	• Seizure frequency
Gernigon, 2017[24] Canada	SR	Unknown	IVIG	Unknown	• Efficacy • Safety • Conditions of use
Vitaliti, 2015[25] Not specified	SR	6 included studies 204 patients with SC	IVIG	Methylprednisolone OR Methylprednisolone tapered with oral Deflazocort OR PLEX OR Standard treatment	Various
		1 included study 30 patients with PANDAS		Placebo (saline solution) OR PLEX	

Author, Publication Date, Country	Study Design	Population[a]	Intervention	Comparator(s)	Outcomes
		3 included studies 63 patients with TS		Prednisolone OR PLEX OR Celecoxib	
		7 included studies 25 patients with ADEM		PLEX OR Methylprednisolone	
		6 included studies 63 patients with MS		Mitoxantrone OR Cyclophosphamide OR Natalizumab OR IFN-band steroid	
		3 included studies 7 patients with Devic's NMO		Rituximab OR Mycofenolate mofetil OR Methylprednisolone OR Azathioprine	
		5 included studies 212 patients with GBS		PLEX OR Supportive treatment OR No treatment	

ADEM = Acute Disseminated Encephalomyelitis, CIDP = Chronic Inflammatory Demyelinating Polyradiculoneuropathy, GBS = Guillain-Barré Syndrome, MG = Myasthenia Gravis, MS = Multiple Sclerosis, NMO = Neuromyelitis Optica, OMS = Opsoclonus-Myoclonus Syndrome; PANDAS = Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections, PLEX = Plasma Exchange, RCT = Randomized Controlled Trial, RS = Rasmussen syndrome, RSE = Refractory Status Epilepticus, SC = Sydenham's Chorea, SR = Systematic Review, TS = Tourette Syndrome.

[a] Number of included studies represents the studies in the systematic review with relevant comparisons for this report.

Table 4: Characteristics of Included Randomized Controlled Trials

Author, Publication Date, Country	Study Design	Population	Intervention	Comparator(s)	Outcomes
Dodel, 2013[27] The United States of America, Germany	RCT	56 adult patients with probable mild-to-moderate AD (aged 50 to 85 years)	2 Week Group IVIG infusions every 2 weeks (0.1, 0.25, or 0.4 grams IVIG per kilograms bodyweight) for 24 weeks 4 Week Group IVIG infusions every 4 weeks (0.2, 0.5, or 0.8 grams IVIG per kilograms bodyweight) for 24 weeks	2 Week Group Placebo (0·9% isotonic sodium chloride) infusions every 2 weeks for 24 weeks 4 Week Group Placebo (0·9% isotonic sodium chloride) infusions every 4 weeks for 24 weeks	Primary: • Median area under the curve of plasma concentration of $A\beta_{1–40}$ between the last infusion and the final visit Secondary: • Area under the curve for plasma concentration of $A\beta_{1–42}$ and of anti-Aβ autoantibodies • Plasma concentration of $A\beta_{1–40}$, $A\beta_{1–42}$, and anti-Aβ autoantibodies at week 24 compared with baseline • Change in cerebral spinal fluid concentration of $A\beta_{1–40}$, $A\beta_{1–42}$, and anti-Aβ autoantibodies • Total tau 24 hours (±8 hours) after last infusion compared with baseline • p-tau_{181} 24 hours (±8 hours) after last infusion compared with baseline • Change in ADAS-Cog at baseline and at week 12 or 24 • Change in the CDR-SB at baseline and at week 12 or 24 • Change in the ADCS-ADL scale at baseline and at week 12 or 24 • Change in MMSE at baseline and at week 12 or 24 • Change in whole brain volume between baseline and week 12 and week 24 • Change in hippocampus volume between baseline and week 12 and week 24 • Change in glucose metabolism between baseline and week 24
van Klink, 2016[28] Netherlands	Follow-up to RCT	66 pediatric patients with RHD (aged 2 to 7 years)	Conventional intensive phototherapy plus prophylactic IVIG (single dose of 0.75	Conventional intensive phototherapy plus placebo (an equal amount of	Primary: • NDI composite outcome, at least one of the following: cerebral palsy, severe cognitive delay, severe motor delay, bilateral deafness requiring

Author, Publication Date, Country	Study Design	Population	Intervention	Comparator(s)	Outcomes
			grams IVIG per kilograms bodyweight administered over 5 to 6 hours starting within the first 4 hours after birth)	a 5% glucose intravenous infusion to match IVIG dosing)	hearing amplification and/or bilateral blindness Secondary: • Presence of allergies • Susceptibility to ear, nose and throat infections
Absoud, 2017[29] The United Kingdom	RCT	2 patients (demographics not reported) Targeted adult patients and pediatric patients with TM and NMO between March 4, 2015 and February 8, 2016	Standard treatment IVMP <u>Adult Patients</u> 1 gram per day for 5 days <u>Pediatric Patients</u> 30 milligrams per kilogram body weight or 500 milligrams per metre squared capped to a maximum dose of 1 gram per day for 5 days PLUS IVIG <u>Adults</u> 2 grams per kilogram body weight administered in five divided doses <u>Children</u> If >41.2 kilograms, 2 grams per kilogram body weight administered in five divided doses If ≤41.2 kilograms, 2	Standard treatment IVMP (intravenous methylprednisolone) <u>Adult Patients</u> 1 gram per day for 5 days <u>Pediatric Patients</u> 30 milligrams per kilogram body weight or 500 milligrams per metre squared capped to a maximum dose of 1 gram per day for 5 days For 12 months	Primary: • Change in ASIA Impairment Scale score from baseline to 6 months post randomization Secondary: • Change in ASIA motor scale and sensory scale scores at 3, 6 and 12 months post randomization • Change in EDSS score at 3, 6 and 12 months post randomization • Change in EQ-5D-Y score at 3, 6 and 12 months post randomization for patients aged 8 to12 years at baseline • Change in EQ-5D-5L score at 3, 6 and 12 months post randomization for patients aged ≥ 13 years at baseline • Change in International SCI-QOL Basic Data Set at 3, 6 and 12 months post randomization for patients aged ≥ 13 years at baseline • Change in Client Service Receipt Inventory (CSRI) 3, 6 and 12 months post randomization Tertiary: • Change in International SCI-QOL, Pain, Bladder and Bowel Function Basic Data Sets at 3, 6 and 12 months post randomization for patients aged ≥ 13 years at baseline • Change in PedsQL Parent Report for Toddlers at 6 and 12 months post randomization for patients aged 2 to 4 years at baseline • Change in PedsQL at 6 and 12 months for patients aged 5 to 7 years at baseline

Author, Publication Date, Country	Study Design	Population	Intervention	Comparator(s)	Outcomes
			grams per kilogram body weight administered in two divided doses For 12 months		• Change in International SCI-QOL Pain Basic Data Set at 6 and 12 months post randomization aged ≥ 13 years at baseline
Kile, 2017[30] The United States of America	RCT	50 adult patients with AD (aged 50 to 84 years)	IVIG of a total dose of 2 grams per kilogram body weight given as 0.4 grams IVIG per kilogram body weight every 2 weeks for 24 months	Placebo (0.9% saline solution) of a total dose of 2 grams per kilogram body weight given as 0.4 grams IVIG per kilogram body weight every 2 weeks for 24 months	Primary: • APCV as measured by MRI at baseline, 12 and 24 months following the first infusion of either 0.4 grams per kilogram body weight of IVIG or 0.9% saline solution every 14 days times 5 infusions Secondary: • Change in cognitive performance between baseline, 12 and 24 months after the first infusion as measured by ADAS-Cog • Change in cognitive performance between baseline, 12 and 24 months after the first infusion as measured by MMSE • Change in cognitive performance between baseline, 12 and 24 months after the first infusion as measured by CDR-SB
Barnett, 2013[31] Canada	Follow-up to RCT	62 adult patients with moderate-to-severe MG (aged 20 to 83 years)	2 grams IVIG per kilogram body weight in two divided doses over two days	PLEX equivalent volume of IV dextrose 5% in water in two divided doses over two days	Primary: • Change in MG-QOL-60 scores at baseline and 2 weeks after treatment • Change in MG-QOL-15 scores at baseline and 2 weeks after treatment
Relkin, 2017[32] The United States of America, Canada	RCT	390 adult patients with mild-to-moderate AD (aged 50 to 89 years) between December 2008 and February 2013	0.2 grams IVIG per kilogram body weight every two weeks for 18 months OR 0.4 grams IVIG per	Placebo (low-dose albumin) equivalent for 18 months	Primary: • Change in ADAS-Cog between baseline and every 3 months through month 18 • Change in ADCS-ADL between baseline, 9 months, and 18 months Secondary: • Change from baseline at 9 months in ADAS-Cog • Change from baseline at 9 months in ADCS-ADL

Author, Publication Date, Country	Study Design	Population	Intervention	Comparator(s)	Outcomes
			kilogram body weight every two weeks for 18 months		• Change from baseline at 9 months in ADCS-CGIC • Change from baseline at 9 months in NPI • Change from baseline at 9 months in QOL-AD
Alipour-Faz, 2017[33] Iran	RCT	24 adult patients (>18 years) with MG prior to thymectomy from 2014 to 2015	1 gram IVIG per kilogram body weight per day for two consecutive days PLUS 50 milligrams Diphenhydramine, 650 milligrams Acetaminophen before infusion 10 to 30 days prior to thymectomy	1 litre of PLEX five times with 5 % albumin replacement fluid every other day 10 to 30 days prior to thymectomy	• Duration of hospitalization stay (days) • Length of ICU stay after surgery (hours) • Length of intubation period (hours) • Duration of surgery (hours) • Dose of steroid administered (milligrams)
Jann, 2012[34] Italy	RCT	20 adult patients (>18 years) with Refractory Neuropathic Pain	Regular drug therapy PLUS 0.4 grams IVIG per kilogram body weight per day for 5 consecutive days (total dose 2 grams IVIG per kilogram body weight)	Regular drug therapy	Primary: • Pain intensity using VAS • Pain intensity using SF-MPQ Secondary: • QOL using the SF-36 questionnaire • QOL using the CGI-C • QOL using the PGI-C • Adverse Events

AD = Alzheimer's disease, ADAS-Cog = Cognitive subscale of the Alzheimer's Disease Assessment Scale, ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Scale, ADCS-CGIC = Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change, APCV = Annualised per cent change in ventricular volume, ASIA = American Spinal Injury Association, CDR-SB = Clinical Dementia Rating -Sum of Boxes, CGI-C = Clinical Global Impression of Change, CSRI = Client Service Receipt Inventory, EDSS = Expanded Disability Status Scale, EQ-5D-Y = EuroQol-5 Dimensions youth version, ICU = Intensive Care Unit, IVIG = Intravenous Immunoglobulin, IVMP = Intravenous Methylprednisolone, MG = Myasthenia Gravis, MG-QOL-60 = Myasthenia Gravis Quality of Life 60-Item Version, MG-QOL-15 = Myasthenia Gravis Quality of Life 15-Item Version, MMSE = Mini-Mental State Examination, MRI = Magnetic Resonance Imaging, NDI = Neurodevelopmental impairment, NMO = Neuromyelitis Optica, NPI = Neuropsychiatric Inventory, PedsQL = Paediatric Quality of Life Inventory, PGI-C = Patient Global Impression of Change, PLEX = Plasma Exchanges, QOL = Quality of Life, QOL-AD = Quality of Life in Alzheimer's Disease Scale, RCT = Randomized Controlled Trial, RHD = Rhesus Hemolytic Disease, SCI-QOL = Spinal Cord Injury Quality of Life, SF-36 = Short Form 36 quality of life questionnaire, SF-MPQ = Short Form McGill Pain Questionnaire, TM = Transverse Myelitis, VAS = Visual Analog Scale.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews with Meta-Analyses using the AMSTAR II Tool[26]

Strengths	Limitations
Geng, 2017[10]	

• The research questions and inclusion criteria for the review included the PICO components of population, intervention, comparator group, and outcome data
• The report of the review contained an explicit statement that the review methods were established prior to the conduct of the review
• Review questions, search strategy, inclusion/exclusion criteria, quality assessment, meta-analysis/synthesis plan, and a plan for investigating heterogeneity were all determined prior to the conduct of the review and any deviations from the protocol were justified
• The review authors explained their selection of both randomized controlled trial and non-randomized studies of interventions study designs for inclusion in the review
• The reviewers used a comprehensive literature search strategy
  ○ Searched reference lists/bibliographies of included studies, searched trial/study registries, included experts, searched for grey literature, conducted search within 24 months of completion of review, searched at least 2 databases, provided word/search strategy, justified publication restrictions
• Review authors performed study selection in duplicate
  ○ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
• Review authors performed data extraction in duplicate
  ○ At least two reviewers achieved consensus on which data to extract from included studies
• Review authors provided a list of all potentially relevant studies that were read in full-text review but were excluded
• Review authors justified the exclusion from the review of each potentially relevant study
• Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and
	• The research questions and inclusion criteria for the review did not include the timeframe for follow-up
	• Review authors did not report on sources of funding for the studies included in this review
	• Only one study met inclusion criteria

Strengths	Limitations
study design for each included study in detail • Review authors assessed the risk of bias in individual studies that were included in the review using the Cochrane Handbook for Systematic Reviews of Interventions risk of bias method and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool • Review authors justified combining the data in a meta-analysis, used an appropriated weighted technique to combine study results and adjust for heterogeneity, as well as found no heterogeneity • Review authors discussed the impact of risk of bias on the results of the meta-analysis or other evidence synthesis • Review authors discussed the impact of risk of bias when interpreting/discussing the results of the review • Review authors found no significant heterogeneity in the results • Review authors discussed the likely impact of publication bias on the results of the review • Review authors described funding sources and reported no competing interests	
Koopman, 2015[11]	
• The research questions and inclusion criteria for the review included the PICO components of population, intervention, comparator group, and outcome data • The report of the review contained an explicit statement that the review methods were established prior to the conduct of the review • Review questions, search strategy, inclusion/exclusion criteria, quality assessment, meta-analysis/synthesis plan, and a plan for investigating heterogeneity were all determined prior to the conduct of the review and any deviations from the protocol were justified • The review authors explained their selection of both randomized controlled trial and quasi-randomized controlled trial study designs for inclusion in the review • The reviewers used a comprehensive literature search strategy ○ Searched reference lists/bibliographies of included studies, searched trial/study registries, included experts, searched for grey literature, conducted search within 24 months of completion of review, searched at least 2 databases, provided word/search strategy, justified publication restrictions	• The research questions and inclusion criteria for the review did not include the timeframe for follow-up • Review authors did not report on sources of funding for the studies included in this review

Strengths	Limitations

• Review authors performed study selection in duplicate
  ○ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
• Review authors performed data extraction in duplicate
  ○ At least two reviewers achieved consensus on which data to extract from included studies
• Review authors provided a list of all potentially relevant studies that were read in full-text review but were excluded
  ○ Review authors justified the exclusion from the review of each potentially relevant study
• Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail
• Review authors assessed the risk of bias in individual studies that were included in the review using the Cochrane Handbook for Systematic Reviews of Interventions risk of bias method and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool
• Review authors justified combining the data in a meta-analysis, used an appropriated weighted technique to combine study results and adjust for heterogeneity, as well as investigated causes of heterogeneity
• Review authors discussed the impact of risk of bias on the results of the meta-analysis or other evidence synthesis
• Review authors discussed the impact of risk of bias when interpreting/discussing the results of the review
• Review authors investigated the causes of heterogeneity and discussed the impact of heterogeneity on the results of the review
• Review authors performed graphical and statistical tests for publication bias and discussed the likely impact of publication bias on the results of the review
• Review authors described funding sources and reported no competing interests	

Lunn, 2016[12]	
• The research questions and inclusion criteria for the review included the PICO components of population, intervention, comparator group, and outcome data • The report of the review contained an explicit statement that the review methods were established prior to the conduct of the review	• The research questions and inclusion criteria for the review did not include the timeframe for follow-up • Review authors did not carry out adequate investigation of publication bias or discuss its likely impact on the results of the review

Strengths	Limitations

• Review questions, search strategy, inclusion/exclusion criteria, quality assessment, meta-analysis/synthesis plan, and a plan for investigating heterogeneity were all determined prior to the conduct of the review and any deviations from the protocol were justified
• The review authors explained their selection of both randomized controlled trial and quasi-randomized controlled trials study design for inclusion in the review
• The reviewers used a comprehensive literature search strategy
  ○ Searched reference lists/bibliographies of included studies, searched trial/study registries, included experts, searched for grey literature, conducted search within 24 months of completion of review, searched at least 2 databases, provided word/search strategy, justified publication restrictions
• Review authors performed study selection in duplicate
  ○ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
• Review authors performed data extraction in duplicate
  ○ At least two reviewers achieved consensus on which data to extract from included studies
• Review authors provided a list of all potentially relevant studies that were read in full-text review but were excluded
  ○ Review authors justified the exclusion from the review of each potentially relevant study
• Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail
• Review authors assessed the risk of bias in individual studies that were included in the review using the Cochrane Handbook for Systematic Reviews of Interventions risk of bias method and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool
• Review authors reported sources of funding for individual studies included in this review
• Review authors justified combining the data in a meta-analysis, used an appropriated weighted technique to combine study results and adjust for heterogeneity, as well as found no heterogeneity
• Review authors discussed the impact of risk of bias on the results of the meta-analysis or other evidence synthesis	

Strengths	Limitations
• Review authors discussed the impact of risk of bias when interpreting/discussing the results of the review • Review authors investigated the causes of heterogeneity and discussed the impact of heterogeneity on the results of the review • Review authors described funding sources and reported no competing interests	
Gajdos, 2012[13]	

• The research questions and inclusion criteria for the review included the PICO components of population, intervention, comparator group, and outcome data
• The report of the review contained an explicit statement that the review methods were established prior to the conduct of the review
• Review questions, search strategy, inclusion/exclusion criteria, quality assessment, meta-analysis/synthesis plan, and a plan for investigating heterogeneity were all determined prior to the conduct of the review and any deviations from the protocol were justified
• The review authors explained their selection of both randomized controlled trial and quasi-randomized controlled trial study designs for inclusion in the review
• The reviewers used a comprehensive literature search strategy
  ○ Searched reference lists/bibliographies of included studies, searched trial/study registries, included experts, searched for grey literature, conducted search within 24 months of completion of review, searched at least 2 databases, provided word/search strategy, justified publication restrictions
• Review authors performed study selection in duplicate
  ○ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
• Review authors performed data extraction in duplicate
  ○ At least two reviewers achieved consensus on which data to extract from included studies
• Review authors provided a list of all potentially relevant studies that were read in full-text review but were excluded
  ○ Review authors justified the exclusion from the review of each potentially relevant study
• Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and
	• The research questions and inclusion criteria for the review did not include the timeframe for follow-up
	• Review authors did not report on sources of funding for the studies included in this review
	• Review authors did not carry out adequate investigation of publication bias or discuss its likely impact on the results of the review

Strengths	Limitations
study design for each included study in detail • Review authors assessed the risk of bias in individual studies that were included in the review using the Cochrane Handbook for Systematic Reviews of Interventions risk of bias method and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool • Review authors justified combining the data in a meta-analysis, used an appropriated weighted technique to combine study results and adjust for heterogeneity, as well as found no heterogeneity • Review authors discussed the impact of risk of bias on the results of the meta-analysis or other evidence synthesis • Review authors discussed the impact of risk of bias when interpreting/discussing the results of the review • Review authors found no significant heterogeneity in the results • Review authors described funding sources and reported no competing interests	
Hughes, 2014[14]	

• The research questions and inclusion criteria for the review included the PICO components of population, intervention, comparator group, and outcome data
• The report of the review contained an explicit statement that the review methods were established prior to the conduct of the review
• Review questions, search strategy, inclusion/exclusion criteria, quality assessment, meta-analysis/synthesis plan, and a plan for investigating heterogeneity were all determined prior to the conduct of the review and any deviations from the protocol were justified
• The review authors explained their selection of both randomized controlled trial and quasi-randomized controlled trial study designs for inclusion in the review
• The reviewers used a comprehensive literature search strategy
  ○ Searched reference lists/bibliographies of included studies, searched trial/study registries, included experts, searched for grey literature, conducted search within 24 months of completion of review, searched at least 2 databases, provided word/search strategy, justified publication restrictions
• Review authors performed study selection in duplicate
  ○ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
	• The research questions and inclusion criteria for the review did not include the timeframe for follow-up
	• Review authors did not report on sources of funding for the studies included in this review
	• Review authors did not carry out adequate investigation of publication bias or discuss its likely impact on the results of the review

Strengths	Limitations

• Review authors performed data extraction in duplicate
  ○ At least two reviewers achieved consensus on which data to extract from included studies
• Review authors provided a list of all potentially relevant studies that were read in full-text review but were excluded
  ○ Review authors justified the exclusion from the review of each potentially relevant study
• Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail
• Review authors assessed the risk of bias in individual studies that were included in the review using the Cochrane Handbook for Systematic Reviews of Interventions risk of bias method and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool
• Review authors justified combining the data in a meta-analysis, used an appropriated weighted technique to combine study results and adjust for heterogeneity, as well as found no heterogeneity
• Review authors discussed the impact of risk of bias on the results of the meta-analysis or other evidence synthesis
• Review authors discussed the impact of risk of bias when interpreting/discussing the results of the review
• Review authors found no significant heterogeneity in the results
• Review authors described funding sources and reported no competing interests	

Iro, 2017[15]	
• The research questions and inclusion criteria for the review included the PICO components of population, intervention, comparator group, outcome data, and timeframe for follow-up • The review authors explained their selection of only the randomized controlled trial study design for inclusion in the review • The reviewers used a comprehensive literature search strategy ○ Searched reference lists/bibliographies of included studies, searched trial/study registries, included experts, searched for grey literature, conducted search within 24 months of completion of review, searched at least 2 databases, provided word/search strategy, justified publication restrictions	• There was no statement that a protocol/review method plan was established prior to review conduct • Review authors did not report on sources of funding for the studies included in this review

Strengths	Limitations

• Review authors performed study selection in duplicate
  ○ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
• Review authors performed data extraction in duplicate
  ○ At least two reviewers achieved consensus on which data to extract from included studies
• Review authors provided a list of all potentially relevant studies that were read in full-text review but were excluded
  ○ Review authors justified the exclusion from the review of each potentially relevant study
• Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail
• Review authors assessed the risk of bias in individual studies that were included in the review using the Cochrane Handbook for Systematic Reviews of Interventions risk of bias method and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool
• Review authors justified combining the data in a meta-analysis, used an appropriated weighted technique to combine study results and adjust for heterogeneity, as well as investigated causes of heterogeneity
• Review authors reduced the impact of risk of bias on the results of the meta-analysis or other evidence synthesis by including only low risk of bias randomized controlled trials
• Review authors reduced the impact of risk of bias when interpreting/discussing the results of the review by including only low risk of bias randomized controlled trials
• Review authors investigated the causes of heterogeneity and discussed the impact of heterogeneity on the results of the review
• Review authors discussed the likely impact of publication bias on the results of the review
• Review authors described funding sources and reported no competing interests	

Huang, 2015[16]	
• The research questions and inclusion criteria for the review included the PICO components of population, intervention, comparator group, outcome data, and timeframe for follow-up	• There was no mention of the reviewers performing study selection in duplicate • Review authors did not provide a list of all potentially relevant studies that

Strengths	Limitations

• The report of the review contained an explicit statement that the review methods were registered prior to the conduct of the review
• Review questions, search strategy, inclusion/exclusion criteria, quality assessment, meta-analysis/synthesis plan, and a plan for investigating heterogeneity were all determined prior to the conduct of the review and any deviations from the protocol were justified
• The review authors explained their selection of both randomized controlled trial and quasi-randomized controlled trial study designs for inclusion in the review
• The reviewers used a comprehensive literature search strategy
  ○ Searched reference lists/bibliographies of included studies, searched trial/study registries, included experts, searched for grey literature, conducted search within 24 months of completion of review, searched at least 2 databases, provided word/search strategy, justified publication restrictions
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• Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail
• Review authors assessed the risk of bias in individual studies that were included in the review using the Cochrane Handbook for Systematic Reviews of Interventions risk of bias method
• Review authors justified combining the data in a meta-analysis, used an appropriated weighted technique to combine study results and adjust for heterogeneity, as well as investigated causes of heterogeneity
• Review authors discussed the impact of risk of bias on the results of the meta-analysis or other evidence synthesis
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• Review authors investigated the causes of heterogeneity and discussed the impact of heterogeneity on the results of the review
• Review authors described funding sources and reported no competing interests
	were read in full-text review but were excluded
	• Review authors did not justify the exclusion from the review of each potentially relevant study
	• Review authors did not report on sources of funding for the studies included in this review
	• Review authors did not carry out adequate investigation of publication bias or discuss its likely impact on the results of the review

Strengths	Limitations
Ortiz-Salas, 2016[17]	

• Reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses
• The research questions and inclusion criteria for the review included the PICO components of population, intervention, comparator group, outcome data, and timeframe for follow-up
• The review authors explained their selection of both randomized controlled trials and non-randomized studies of interventions study designs for inclusion in the review
• The reviewers used a comprehensive literature search strategy
  ○ Searched reference lists/bibliographies of included studies, searched trial/study registries, included experts, searched for grey literature, conducted search within 24 months of completion of review, searched at least 2 databases, provided word/search strategy, justified publication restrictions
• Review authors performed study selection in duplicate
  ○ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
• Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail
• Review authors assessed the risk of bias in individual studies that were included in the review using the Oxford Centre for Evidence-based Medicine 2011 criteria for levels of evidence
• Review authors justified combining the data in a meta-analysis, used an appropriated weighted technique to combine study results and adjust for heterogeneity, as well as investigated causes of heterogeneity
• Review authors discussed the impact of risk of bias on the results of the meta-analysis or other evidence synthesis
• Review authors discussed the impact of risk of bias when interpreting/discussing the results of the review
• Review authors investigated the causes of heterogeneity and discussed the impact of heterogeneity on the results of the review
• Review authors performed graphical and statistical tests for publication bias and discussed the likely impact of publication bias on the results of the review
	• There was no statement that a protocol/review method plan was established prior to review conduct
	• There was no mention of the reviewers performing data extraction in duplicate
	• Review authors did not provide a list of all potentially relevant studies that were read in full-text review but were excluded
	• Review authors did not justify the exclusion from the review of each potentially relevant study
	• Review authors did not report on sources of funding for the studies included in this review

Strengths	Limitations
• Review authors reported no competing interests	
Racosta, 2017[18]	
• Reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses • The research questions and inclusion criteria for the review included population, intervention, comparator group, and outcome data components • The review authors explained their selection of both randomized controlled trial and non-randomized studies of interventions study designs for inclusion in the review • The reviewers used a fairly comprehensive literature search strategy ○ Searched reference lists/bibliographies of included studies, searched for grey literature, searched at least 2 databases, provided word/search strategy, justified publication restrictions • One reviewer extracted data and two reviewers reviewed the extracted data • Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail • Review authors assessed the risk of bias in individual studies that were included in the review using the Newcastle-Ottawa Scale (NOS) • Review authors justified combining the data in a meta-analysis, used an appropriated weighted technique to combine study results and adjust for heterogeneity, as well as investigated causes of heterogeneity • Review authors discussed the impact of risk of bias on the results of the meta-analysis or other evidence synthesis • Review authors discussed the impact of risk of bias when interpreting/discussing the results of the review • Review authors investigated the causes of heterogeneity and discussed the impact of heterogeneity on the results of the review • Review authors performed graphical and statistical tests for publication bias and discussed the likely impact of publication bias on the results of the review	• The research questions and inclusion criteria for the review did not include the timeframe for follow-up • There was no statement that a protocol/review method plan was established prior to review conduct • Reviewers did not search trial/study registries or include/consult experts in the field • There was no mention of the reviewers performing study selection in duplicate • Review authors did not provide a list of all potentially relevant studies that were read in full-text review but were excluded • Review authors did not justify the exclusion from the review of each potentially relevant study • Review authors did not report on sources of funding for the studies included in this review • Review authors did not address conflict of interest or funding
Olyaeemanesh, 2016[19]	
• The research questions and inclusion criteria for the review included population, intervention, comparator group, and outcome data components	• The research questions and inclusion criteria for the review did not include the timeframe for follow-up

Strengths	Limitations
• The review authors explained their selection of only the randomized controlled trial study design for inclusion in the review • The reviewers used a comprehensive literature search strategy ○ Searched reference lists/bibliographies of included studies, searched trial/study registries, included experts, searched for grey literature, conducted search within 24 months of completion of review, searched at least 2 databases, provided word/search strategy, justified publication restrictions • Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail • Review authors assessed the risk of bias in individual studies that were included in the review using the Cochrane Handbook for Systematic Reviews of Interventions risk of bias method for selection bias, performance bias, attrition bias, and detection bias as well as the Jadad checklist • Review authors justified combining the data in a meta-analysis, used an appropriated weighted technique to combine study results and adjust for heterogeneity, as well as investigated causes of heterogeneity • Review authors reduced the impact of risk of bias on the results of the meta-analysis or other evidence synthesis by including only low risk of bias randomized controlled trials • Review authors reduced the impact of risk of bias when interpreting/discussing the results of the review by including only low risk of bias randomized controlled trials	• There was no statement that a protocol/review method plan was established prior to review conduct • There was no mention of the reviewers performing study selection in duplicate • There was no mention of the reviewers performing data extraction in duplicate • Review authors did not provide a list of all potentially relevant studies that were read in full-text review but were excluded • Review authors did not justify the exclusion from the review of each potentially relevant study • Review authors did not report on sources of funding for the studies included in this review • Review authors did not discuss the impact of risk of bias on the results of the meta-analysis or other evidence synthesis • Review authors did not discuss the impact of risk of bias when interpreting/discussing the results of the review • Review authors did not discuss the impact of heterogeneity when interpreting/discussing the results of the review • Review authors did not carry out adequate investigation of publication bias or discuss its likely impact on the results of the review • Review authors did not address conflict of interest or funding
Al Amrani, 2017[20]	
• The research questions and inclusion criteria for the review included population, intervention, comparator group, and outcome data components • The reviewers used a fairly comprehensive literature search strategy ○ Searched reference lists/bibliographies of included studies, searched for grey literature, searched at least 2 databases, provided word/search strategy, justified publication restrictions • Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail • Review authors justified combining the raw data in a meta-analysis • Review authors reported no competing interests	• The research questions and inclusion criteria for the review did not include the timeframe for follow-up • There was no statement that a protocol/review method plan was established prior to review conduct • There was no explanation for inclusion of different study designs • Reviewers did not search trial/study registries or include/consult experts in the field • There was no mention of the reviewers performing study selection in duplicate • There was no mention of the reviewers performing data extraction in duplicate • Review authors did not provide a list of all potentially relevant studies that

Strengths	Limitations
	were read in full-text review but were excluded • Review authors did not justify the exclusion from the review of each potentially relevant study • Review authors did not assess risk of bias in studies included in the review • Review authors did not report on sources of funding for the studies included in this review • Review authors did not discuss the impact of risk of bias on the results of the meta-analysis or other evidence synthesis • Review authors did not discuss the impact of risk of bias when interpreting/discussing the results of the review • Review authors did not discuss the impact of heterogeneity when interpreting/discussing the results of the review • Review authors did not carry out adequate investigation of publication bias or discuss its likely impact on the results of the review

Table 6: Strengths and Limitations of Systematic Reviews without Meta-Analyses using the AMSTAR II Tool[26]

Strengths	Limitations
Gogou, 2017[21]	

• The research questions and inclusion criteria for the review included the PICO components of population, intervention, comparator group, outcome data, and timeframe for follow-up
• The review authors explained their selection of both randomized controlled trial and non-randomized studies of interventions study designs for inclusion in the review
• Review authors performed study selection in duplicate
  ○ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
• Review authors performed data extraction in duplicate
  ○ At least two reviewers achieved consensus on which data to extract from included studies
• Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail
• Review authors assessed the risk of bias in individual studies that were included in the review using the Cochrane Handbook for Systematic Reviews of Interventions risk of bias method
• Review authors discussed the impact of risk of bias when interpreting/discussing the results of the review
• Review authors investigated the causes of heterogeneity and discussed the impact of heterogeneity on the results of the review
• Review authors described funding sources and reported no competing interests
	• There was no statement that a protocol/review method plan was established prior to review conduct
	• Review authors did not provide a list of all potentially relevant studies that were read in full-text review but were excluded
	• Review authors did not justify the exclusion from the review of each potentially relevant study
	• Review authors did not report on sources of funding for the studies included in this review

Zeiler, 2017[22]	
• Reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses • The research questions and inclusion criteria for the review included the PICO components of population, intervention, comparator group, and outcome data	• The research questions and inclusion criteria for the review did not include the timeframe for follow-up • There was no statement that a protocol/review method plan was established prior to review conduct • There was no mention of the reviewers performing data extraction in duplicate

Strengths	Limitations

• The review authors explained their selection of both randomized controlled trial and non-randomized studies of interventions study designs for inclusion in the review
• The reviewers used a comprehensive literature search strategy
  ○ Searched reference lists/bibliographies of included studies, searched trial/study registries, included experts, searched for grey literature, conducted search within 24 months of completion of review, searched at least 2 databases, provided word/search strategy, justified publication restrictions
• Review authors performed study selection in duplicate
  ○ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
• Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail
• Review authors assessed the risk of bias in individual studies that were included in the review using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool as well as Oxford criteria
• Review authors discussed the impact of risk of bias when interpreting/discussing the results of the review
• Review authors investigated the causes of heterogeneity and discussed the impact of heterogeneity on the results of the review
• Review authors reported no competing interests
	• Review authors did not provide a list of all potentially relevant studies that were read in full-text review but were excluded
	• Review authors did not justify the exclusion from the review of each potentially relevant study
	• Review authors did not report on sources of funding for the studies included in this review

Gadian, 2017[23]	
• The research questions and inclusion criteria for the review included the PICO components of population, intervention, comparator group, and outcome data • The review authors explained their selection of both randomized controlled trial and non-randomized studies of interventions study designs for inclusion in the review • The reviewers searched reference lists/bibliographies of included studies • Review authors performed study selection in duplicate • At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include • One reviewer extracted data and another reviewer verified the extracted data • Review authors described the PICOTS components of population,	• The research questions and inclusion criteria for the review did not include the timeframe for follow-up • There was no statement that a protocol/review method plan was established prior to review conduct • The reviewers only searched one database and did not search trial/study registries, include/consult experts in the field, or search for grey literature • Review authors did not provide a list of all potentially relevant studies that were read in full-text review but were excluded • Review authors did not justify the exclusion from the review of each potentially relevant study • Review authors did not report on sources of funding for the studies included in

Strengths	Limitations
intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail • Review authors assessed the risk of bias in individual studies that were included in the review using the Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence • Review authors discussed the impact of risk of bias when interpreting/discussing the results of the review • Review authors investigated the causes of heterogeneity and discussed the impact of heterogeneity on the results of the review • Review authors described funding sources	this review • Review authors did not describe how competing interests from funding sources were managed
Gernigon, 2017[24]	
• The research questions and inclusion criteria for the review included population, intervention, comparator group, and outcome data components • Review questions, search strategy, inclusion/exclusion criteria, quality assessment were all determined prior to the conduct of the review • The review authors explained their selection of only the randomized controlled trial study design for inclusion in the review • The reviewers used a comprehensive literature search strategy o Searched reference lists/bibliographies of included studies, searched trial/study registries, included experts, searched for grey literature, conducted search within 24 months of completion of review, searched at least 2 databases, provided word/search strategy, justified publication restrictions • Review authors performed study selection in duplicate o At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include • One reviewer extracted data and another reviewer verified the extracted data • Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail • Review authors described funding sources and reported no competing interests	• The research questions and inclusion criteria for the review did not include the timeframe for follow-up • Review authors did not provide a list of all potentially relevant studies that were read in full-text review but were excluded • Review authors did not justify the exclusion from the review of each potentially relevant study • Review authors did not assess risk of bias in studies included in the review • Review authors did not report on sources of funding for the studies included in this review • Review authors did not discuss the impact of risk of bias when interpreting/discussing the results of the review • Review authors did not discuss the impact of heterogeneity when interpreting/discussing the results of the review
Vitaliti, 2015[25]	
• The research questions and inclusion criteria for the review included the PICO	• The research questions and inclusion criteria for the review did not include the

Strengths	Limitations

components of population, intervention, comparator group, and outcome data
• The review authors explained their selection of both randomized controlled trial and non-randomized studies of interventions study designs for inclusion in the review
• The reviewers used a comprehensive literature search strategy
  ○ Searched at least 2 databases, provided word/search strategy, justified publication restrictions
• Review authors performed study selection in duplicate
  ○ At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
• Review authors described the PICOTS components of population, intervention, comparator group, outcome data, timeframe for follow-up, and study design for each included study in detail
• Review authors reported no competing interests
	timeframe for follow-up
	• There was no statement that a protocol/review method plan was established prior to review conduct
	• Reviewers did not search reference lists/bibliographies of included studies, search trial/study registries, include/consult experts in the field, or search for grey literature
	• There was no mention of the reviewers performing data extraction in duplicate
	• Review authors did not provide a list of all potentially relevant studies that were read in full-text review but were excluded
	• Review authors did not justify the exclusion from the review of each potentially relevant study
	• Review authors did not assess risk of bias in studies included in the review
	• Review authors did not report on sources of funding for the studies included in this review
	• Review authors did not discuss the impact of risk of bias when interpreting/discussing the results of the review
	• Review authors did not discuss the impact of heterogeneity when interpreting/discussing the results of the review

Table 7: Strengths and Limitations of Randomized Controlled Trials using the Cochrane Risk of Bias tool for RCTs[35] and the External Validity Component of the Downs and Black Checklist[36]

Strengths	Limitations
Dodel, 2013[27]	

• Sequence Generation (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Investigators describe a random component in the sequence generation process: computer-generated web-based 8-block randomization
• Allocation Concealment (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Participants and investigators enrolling participants could not foresee assignments because of central allocation (web-based randomization) and masking of drug through use of opaque pouches
• Blinding (Performance Bias and Detection Bias)
  ○ Definitely Low Risk of Bias
  ○ Participants, key study personnel, and outcome assessors were blinded but statistician was not, non-blinding of statistician is unlikely to introduce bias
• Incomplete Outcome Data (Attrition Bias)
  ○ Definitely Low Risk of Bias
  ○ Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
• Selective Outcome Reporting (Reporting Bias)
  ○ Definitely Low Risk of Bias
  ○ The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes have been reported in the pre-specified way
• External Validity
  ○ Subjects who were prepared to participate were representative of the entire population from which they were recruited
  ○ Staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive
	• Other Sources of Bias
	  ○ Probably High Risk of Bias
	  ○ Industry involvement in study design, data interpretation, writing of manuscript, and decision to publish. No involvement in data collection.
	• External Validity
	  ○ Unable to determine if the subjects asked to participate in the study were representative of the entire population from which they were recruited

Strengths	Limitations
van Klink, 2016[28]	

• Sequence Generation (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Investigators describe a random component in the sequence generation process: computer-generated block randomization
• Allocation Concealment (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Participants and investigators enrolling participants could not foresee assignments because of identical coded drug boxes, sequentially numbered identical vials containing infusion solutions
• Blinding (Performance Bias and Detection Bias)
  ○ Probably Low Risk of Bias
  ○ Participants, key study personnel, and outcome assessors were blinded in the original trial, but only participants were blinded in this follow-up
• Incomplete Outcome Data (Attrition Bias)
  ○ Definitely Low Risk of Bias
  ○ Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
• Other Sources of Bias
  ○ Definitely Low Risk of Bias
  ○ The study appears to be free of other sources of bias
• External Validity
  ○ Subjects who were prepared to participate were representative of the entire population from which they were recruited
	• Selective Outcome Reporting (Reporting Bias)
	  ○ Probably High Risk of Bias
	  ○ The study protocol is available but this is a long-term follow-up with new outcomes
	• External Validity
	  ○ Unable to determine if the subjects asked to participate in the study were representative of the entire population from which they were recruited
	  ○ Staff, places, and facilities where the patients were treated were not representative of the treatment the majority of patients receive

Absoud, 2017[29]	

• Sequence Generation (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Investigators describe a random component in the sequence generation process: stratified block randomization with the block randomly varying in size and stratification by adult/child
• Allocation Concealment (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Participants and investigators enrolling participants could not foresee
	• Other Sources of Bias
	  ○ Definitely High Risk of Bias
	  ○ Industry Funding and Low Study Recruitment (2 recruited out of 170 needed)
	• External Validity
	  ○ Unable to determine if the subjects asked to participate in the study were representative of the entire population from which they were recruited

Strengths	Limitations
assignments because of central allocation (web-based randomization) • Blinding (Performance Bias and Detection Bias) ○ Definitely Low Risk of Bias ○ Participants and key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others is unlikely to introduce bias • Incomplete Outcome Data (Attrition Bias) ○ Definitely Low Risk of Bias ○ No Missing Outcome Data • Selective Outcome Reporting (Reporting Bias) ○ Definitely Low Risk of Bias ○ The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes have been reported in the pre-specified way	○ Subjects who were prepared to participate were not representative of the entire population from which they were recruited ○ Staff, places, and facilities where the patients were treated were not representative of the treatment the majority of patients receive
Kile, 2017[30]	
• Sequence Generation (Selection Bias) ○ Definitely Low Risk of Bias ○ Investigators describe a random component in the sequence generation process: computer-generated 4-block randomization • Allocation Concealment (Selection Bias) ○ Definitely Low Risk of Bias ○ Participants and investigators enrolling participants could not foresee assignments because fluid and tubing of infusion were concealed with protective covering • Blinding (Performance Bias and Detection Bias) ○ Definitely Low Risk of Bias ○ Participants, key study personnel, and outcome assessors were blinded • External Validity ○ Subjects who were prepared to participate were representative of the entire population from which they were recruited	• Incomplete Outcome Data (Attrition Bias) ○ Probably High Risk of Bias ○ Insufficient information to permit judgement • Selective Outcome Reporting (Reporting Bias) ○ Probably High Risk of Bias ○ The study protocol is available and but not all of the study's pre-specified (primary and secondary) outcomes have been reported in the pre-specified way • Other Sources of Bias ○ Probably High Risk of Bias ○ Industry involvement in funding trial and providing study drugs • External Validity ○ Unable to determine if the subjects asked to participate in the study were representative of the entire population from which they were recruited ○ Staff, places, and facilities where the patients were treated were not representative of the treatment the majority of patients receive

Strengths	Limitations
Barnett, 2013[31]	

• Sequence Generation (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Investigators describe a random component in the sequence generation process: computer-generated 4-block randomization
• Allocation Concealment (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Participants and investigators enrolling participants could not foresee assignments because solutions in opaque bottles indistinguishable to the nursing staff, patients, and treating physicians
• Blinding (Performance Bias and Detection Bias)
  ○ Probably Low Risk of Bias
  ○ Participants, key study personnel, and outcome assessors were blinded
• Incomplete Outcome Data (Attrition Bias)
  ○ Definitely Low Risk of Bias
  ○ No Missing Outcome Data
• External Validity
  ○ Subjects who were prepared to participate were representative of the entire population from which they were recruited
	• Selective Outcome Reporting (Reporting Bias)
	  ○ Probably High Risk of Bias
	  ○ The study protocol is available but this is a long-term follow-up with new outcomes
	• Other Sources of Bias
	  ○ Probably High Risk of Bias
	  ○ Industry funding through unrestricted educational grant
	• External Validity
	  ○ Unable to determine if the subjects asked to participate in the study were representative of the entire population from which they were recruited
	  ○ Unable to determine if the staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive

Relkin, 2017[32]	

• Sequence Generation (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Investigators describe a random component in the sequence generation process: stratified permuted block randomization
• Blinding (Performance Bias and Detection Bias)
  ○ Probably Low Risk of Bias
  ○ Blinding is not described in detail but it is clear that appropriate blinding has been used
• Incomplete Outcome Data (Attrition Bias)
  ○ Definitely Low Risk of Bias
  ○ Missing outcome data have been imputed using multiple imputation
• Selective Outcome Reporting (Reporting Bias)
  ○ Definitely Low Risk of Bias
  ○ The study protocol is available and all of the study's pre-specified
	• Allocation Concealment (Selection Bias)
	  ○ Probably High Risk of Bias
	  ○ Insufficient information to permit judgement
	• Other Sources of Bias
	  ○ Probably High Risk of Bias
	  ○ Industry involvement in funding trial, providing study drugs, study design, and analyses
	• External Validity
	  ○ Unable to determine if the subjects asked to participate in the study were representative of the entire population from which they were recruited
	  ○ Unable to determine if the staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive

Strengths	Limitations
(primary and secondary) outcomes have been reported in the pre-specified way • External Validity ○ Subjects who were prepared to participate were representative of the entire population from which they were recruited	
Alipour-Faz, 2017[33]	

• Sequence Generation (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Investigators describe a random component in the sequence generation process: simple randomization
• Incomplete Outcome Data (Attrition Bias)
  ○ Definitely Low Risk of Bias
  ○ No Missing Outcome Data
• Other Sources of Bias
  ○ Definitely Low Risk of Bias
  ○ The study appears to be free of other sources of bias
• External Validity
  ○ Subjects who were prepared to participate were representative of the entire population from which they were recruited
  ○ Staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive
	• Allocation Concealment (Selection Bias)
	  ○ Probably High Risk of Bias
	  ○ Insufficient information to permit judgement
	• Blinding (Performance Bias and Detection Bias)
	  ○ Definitely High Risk of Bias
	  ○ No blinding and outcomes are likely to be influenced by lack of blinding
	• Selective Outcome Reporting (Reporting Bias)
	  ○ Probably High Risk of Bias
	  ○ Insufficient information to permit judgement
	• External Validity
	  ○ Unable to determine if the subjects asked to participate in the study were representative of the entire population from which they were recruited

Jann, 2012[34]	

• Sequence Generation (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Investigators describe a random component in the sequence generation process: computer-generated block randomization
• Allocation Concealment (Selection Bias)
  ○ Definitely Low Risk of Bias
  ○ Participants and investigators enrolling participants could not foresee assignments because of central allocation
• Incomplete Outcome Data (Attrition Bias)
  ○ Definitely Low Risk of Bias
  ○ Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
	• Blinding (Performance Bias and Detection Bias)
	  ○ Definitely High Risk of Bias
	  ○ No blinding and outcomes are likely to be influenced by lack of blinding
	• Selective Outcome Reporting (Reporting Bias)
	  ○ Probably High Risk of Bias
	  ○ Insufficient information to permit judgement
	• Other Sources of Bias
	  ○ Probably High Risk of Bias
	  ○ Industry involvement in supply of intervention product, statistical analysis (provided independent statistician), and writing of manuscript

Strengths	Limitations

• External Validity
  ○ Subjects who were prepared to participate were representative of the entire population from which they were recruited
  ○ Staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients receive
	• External Validity
	Unable to determine if the subjects asked to participate in the study were representative of the entire population from which they were recruited

Appendix 4: Main Study Findings and Author's Conclusions

Table 8: Summary of Findings of Included Systematic Reviews with Meta-Analyses

Main Study Findings	Author's Conclusion
Geng, 2017[10]	

• 50% or greater reduction in seizure frequency
  ○ No difference between IVIG and placebo groups: Risk ratio 1.76 (0.79 to 3.93) p=0.17
• Incidence or severity of adverse effects
  ○ Not reported
• Global assessment
  ○ Significant difference IVIG group versus placebo group: Risk ratio 3.21 (1.10 to 9.36) p=0.033
	"Implications for practice
	• No reliable conclusions can be drawn at present regarding the effects of intravenous immunoglobulin (IVIG) as a treatment for epilepsy.
	Implications for research …
	• 1. Randomized controlled trials (RCTs) are needed to investigate the effects of IVIG in epileptic patients.
	• 2. The efficacy of IVIG treatment among a homogenous subset of patients with refractory epilepsy is unclear and could be assessed by future research.
	• 3. Reporting of RCTs should be according to the CONSORT Statement (Schulz 2010) to enable readers to judge the reliability and relevance of the findings.
	• 4. Large sample sizes, with statistical power to detect a clinically significant difference, should be taken into consideration.
	• 5. Studies should be performed to determine the optimal dose of IVIG.
	• 6. Control treatments may include antiepileptic drugs.
	• 7. Studies should be designed to allow for assessment of long-term effects and adverse events.
	• 8. Future trials should include all clinically relevant outcomes (not only the seizure endpoints) to provide sufficient evidence.
	• 9. Given the protective role of IVIG in the immune system, whether IVIG may have some effects on epilepsy caused by antibodies deserves further investigation." [10] page 12

Koopman, 2015[11]	

• (Change from baseline) Activity limitations ≤3 months –Measured with the SF-36 PCS1 (scale from 0 to 100)
  ○ The mean (change in) activity limitations in the intervention groups was 2.35 higher (0.06 lower to 4.76 higher)
  ○ The mean activity limitations in one control group was 33.3
	"Due to insufficient good-quality data and lack of randomised studies, it was impossible to draw definite conclusions about the effectiveness of interventions for PPS. Results indicated that IVIG, lamotrigine, muscle strengthening exercises and static magnetic fields may be beneficial but need further investigation to clarify whether any real and meaningful effect exists." [11] page 2

Main Study Findings	Author's Conclusion
○ The mean change in activity limitations in one control group was -0.8 • Activity limitations > 3 months –Measured with the SF-36 PCS1 (scale from 0 to 100) ○ Activity limitations in the intervention groups was 0.51 lower (4.63 lower to 3.60 higher) ○ The mean activity limitations in the control groups was 33.9 • Adverse events ○ Insufficient reporting	"IVIG is a treatment in which antibodies that have been purified from donated blood are given as an infusion into a vein over a period of time. There was moderate- and low-quality evidence that IVIG has no beneficial effect on activity limitations in the short term and long term, respectively. Evidence for effectiveness on muscle strength was inconsistent, as results differed across studies. IVIG caused minor side effects in a substantial proportion of the participants." [11] page 2
Lunn, 2016[12]	
• Change in Clinical Neuropathy Disability Score (CNDS) between baseline and six months ○ Planned outcome in methods; no data available at six months • Subjective score at six months ○ Planned outcome in methods; no data available at six months • Number of participants improved by at least 20% on NSI at 6 months ○ Planned outcome in methods; no data available at six months	"There is inadequate reliable evidence from trials of immunotherapies in anti-MAG paraproteinaemic neuropathy to form an evidence base supporting any particular immunotherapy treatment. IVIG has a statistically but probably not clinically significant benefit in the short term. The meta-analysis of two trials of rituximab provides, however, low-quality evidence of a benefit from this agent. The conclusions of this meta-analysis await confirmation, as one of the two included studies is of very low quality. We require large well-designed randomised trials of at least 12 months' duration to assess existing or novel therapies, preferably employing unified, consistent, well-designed, responsive, and valid outcome measures."[12] page 2 "Two trials with 22 and 11 participants (20 with antibodies against MAG) suggest that IVIG may sometimes produce short-term measurable benefit and is relatively safe, but the benefit is of doubtful clinical significance. No severe adverse effects related to IVIG were reported in these trials."[12] page 3
Gajdos, 2012[13]	
Placebo • No change in QMGS day 0 to 14 ○ Mean difference -1.60 (-3.23 to 0.03) • No change in QMGS day 0 to 28 ○ Mean difference -1.80 (-3.64 to 0.04) • No change in QMGS day 0 to day 42 for severe stable myasthenia gravis ○ Mean difference 1.60 (-1.92 to 5.12) • Slight change in MG-ADL day 0 to 42 for severe stable myasthenia gravis ○ Mean difference 2.30 (0.06 to 4.54) Plasma exchange	"In exacerbation of myasthenia gravis, one RCT of IVIG versus placebo showed some evidence of the efficacy of IVIG and two did not show a significant difference between IVIG and plasma exchange. Another showed no significant difference in efficacy between 1 g/kg and 2 g/kg of IVIG. A further, but underpowered, trial showed no significant difference between IVIG and oral methylprednisolone. In chronic myasthenia gravis, there is insufficient evidence from RCTs to determine whether IVIG is efficacious."[13] page 2 "Implications for practice: In myasthenia gravis worsening, one RCT of IVIG versus placebo showed some evidence of the efficacy of IVIG and two did not show a significant difference between IVIG and plasma exchange in severe myasthenia gravis

Main Study Findings	Author's Conclusion

• No change in MMS day 0 to 15
  ○ Mean difference -1.00 (-7.72 to 5.72)
• No change in QMGS day 0 to day 14 for worsening myasthenia gravis
  ○ Mean difference -1.50 (-3.43 to 0.43)
• Slight change in QMGS day 0 to day 21 for worsening myasthenia gravis
  ○ Mean difference -2.00 (-3.98 to -0.02)
• No change in QMGS day 0 to day 28 for worsening myasthenia gravis
  ○ Mean difference -2.10 (-4.20 to 0.00)
Methylprednisolone
• No change in QMGS day 0 to 14
  ○ Mean difference -0.42 (-1.20 to 0.36)
	worsening or with exacerbation. Another showed no significant difference in efficacy between 1 g/kg and 2 g/kg of IVIG. A further, yet underpowered, trial showed no significant difference between IVIG and oral methylprednisolone. In chronic (moderate or severe but stable) myasthenia gravis, there is insufficient evidence from RCTs to determine whether IVIG is efficacious."[13] page 12
	
	"Implications for research: Further RCTs are needed to confirm the effectiveness of IVIG compared to plasma exchange for the treatment of MG crisis and to determine the indications for IVIG in moderate and severe but stable MG. More research is needed to determine whether IVIG improves MG in the perioperative period or reduces the need for corticosteroids as suggested by case series."[13] page 12

Hughes, 2014[14]	
"Three studies in children suggested that IVIG speeds up recovery compared with supportive care. Only one used the disability scale. They provided low quality evidence"[14] page 3 "In one small trial in children, the effect on disability appeared similar with a standard dose over two days rather than five days"[14] page 3	"Implications for practice … In children, low quality evidence suggests that IVIG hastens recovery compared with supportive care alone."[14] page 22 "Implications for research randomised trials are needed to decide whether IVIG helps in mild GBS, and in disease that has lasted more than two weeks. Randomised trials also need to establish the optimal dose. Future trials would be helped by agreement on criteria for recording adverse events and the validation of recently developed potentially more sensitive outcome measures."[14] page 22
Iro, 2017[15]	

Primary:
• No significant disability at 3 to 6 months between IVIG and placebo
  ○ Risk ratio 0.75 (0.22 to 2.60)
• No difference in risk of ≥ 1 serious adverse event between IVIG and placebo
  ○ Risk ratio 1.00 (0.07 to 14.05)
• No difference in risk of mortality between IVIG and placebo
  ○ Risk ratio 0.50 (0.05 to 4.75)
• No difference in risk of hypotension between IVIG and placebo or standard care
  ○ Risk ratio 1.00 (0.07 to 14.05)
• No difference in risk of melaena between IVIG and placebo or standard care
  ○ Risk ratio 1.00 (0.07 to 14.05)
• No difference in significant disability at discharge between IVIG and placebo
	"The findings suggest a clinical benefit of adjunctive IVIG treatment for children with viral encephalitis for some clinical measures (i.e. mean length of hospital stay, time (days) to stop spasms, time to regain consciousness, and time to resolution of neuropathic symptoms and fever. For children with Japanese encephalitis, IVIG had a similar effect to placebo when assessing significant disability and serious adverse events. Despite these findings, the risk of bias in the included studies and quality of the evidence make it impossible to reach any firm conclusions on the efficacy and safety of IVIG as add-on treatment for children with encephalitis. Furthermore, the included studies involved only children with viral encephalitis, therefore findings of this review cannot be generalised to all forms of encephalitis. Future well-designed RCTs are needed to assess the efficacy and safety of IVIG in the management of children with all forms of encephalitis. There is a need for internationally agreed core outcome measures for clinical trials in childhood encephalitis."[15] page 2

Main Study Findings	Author's Conclusion
○ Risk ratio 1.00 (0.60 to 1.67) • IVIG decreases length of hospital stay over standard care ○ Risk ratio -4.54 (-7.47 to -1.61) • IVIG decreases length of hospital stay over interferon ○ Risk ratio -0.57 (-0.99 to -0.15)	"The quality of evidence in the included studies was very low, making it impossible to draw any firm and definite conclusions on the clinical efficacy and safety of IVIG treatment for children with encephalitis. Furthermore, there was no information on funding while, for one study, the main authors' group was affiliated to the funding body: this is a well-known potential source of conflict of interest and thus of bias."[15] page 3
Huang, 2015[16]	
• No difference in pain severity between IVIG and placebo ○ Weighted mean difference -1.02 (-2.51 to 0.47) • No difference in fatigue scores between IVIG and placebo ○ Weighted mean difference 0.28 (-0.56 to 1.12) • No difference in muscle strength between IVIG and placebo	"Although we observed statistically significant differences in the pain scores in each individual prospective trial, our meta-analysis of the RCTs indicated that the administration of IVIG treatment for PPS is unlikely to produce a significant reduction in the pain and fatigue severity, and improvement of muscle strength. Overall, the methodological quality of the reviewed studies was not adequate. Regarding the cost benefit, we cannot recommend the routine administration of IVIG for patients with PPS, but it could serve as a supportive treatment option for patient subgroups with moderate to severe PPS. Additional large, long-term RCTs are required to further evaluate the responding subgroups, long-term effects, and dosing schedules."[16] page 8
Ortiz-Salas, 2016[17]	
• No clinical efficacy of PLEX versus IVIG for MG ○ Odds ratio 0.561 (0.224 to 1.408) • Adverse Events ○ Odds ratio 0.654 (0.166 to 2.572)	"There is no evidence for superiority in the efficacy or safety of immunoglobulin or plasmapheresis in the management of … myasthenia gravis. However, caution should be exercised in the interpretation of these results given the limitations in the quality of the evidence and the heterogeneity of the studies."[17] page 1
Racosta, 2017[18]	
• Medical Research Council Sum Score (MRC-SS) for muscle strength ○ No difference between SCIG and IVIG groups for MMN mean difference 0.65 (-0.31 to 1.61) ○ No difference between SCIG and IVIG groups for CIDP mean difference 0.84 (-0.01 to 1.69)	"In conclusion, based on its comparable efficacy and seemingly better safety profile, [SCIG] could be considered as a valid alternative to IVIG in patients with CIDP and MMN, particularly in patients who experience frequent fluctuations or cannot tolerate IVIG despite adjustments to the frequency and doses of infusions."[18] page 809
Olyaeemanesh, 2016[19]	
• No change in EDSS from baseline ○ Mean difference -0.05 (-0.29 to 0.18)	"IVIG can be considered as an alternative therapeutic option, second-line therapy or adjuvant therapy, considering its beneficial effects (high tolerance, need to be injected with longer intervals, etc.) for treating relapsing–remitting MS patients."[19] page 1

Main Study Findings	Author's Conclusion
	"Although studies have shown beneficial effects of immunoglobulin in measuring variable diseases activities, the evidence, with regards to the short duration and the number of participants in the trials, was not sufficient, and more accurate assessment of the patients is needed."[19] page 10
Al Amrani, 2017[20]	

• IVIG reduced seizure frequency ($p<0.05$)
• Reduction of seizure frequency for median 3.7 years
• No serious adverse events
• Two mild adverse events
  ○ Post-infusion paresthesia (n = 1)
  ○ Transient increase in temperature (n = 1)
	"Despite obvious limitations, mainly because of the small number of patients, and the selection biases, this study suggests that, based on the available data, IVIG might be effective in the treatment of intractable epilepsy secondary to focal cortical dysplasia. Further therapeutic trials are mandatory to further clarify the efficacy of IVIG in this condition."[20] page 79
	
	"Altogether, the few observational studies we found from the literature suggest that in most centers, IVIG is not used for the treatment of intractable epilepsy arising from FCD. Centers using IVIG for the treatment of intractable epilepsy caused by FCD did not perform the procedure in a way to accumulate data that would much improve the level of evidence (class IV studies). Given the persistent clinical equipoise for IVIG treatments of intractable epilepsy caused by FCD, prospective controlled studies about the benefit-risk are recommended. The data we gathered provide milestones to guide such prospective studies."[20] page 81

CIDP = Chronic Inflammatory Demyelinating Polyneuropathy, CNDS = Clinical Neuropathy Disability Score, EDSS = Expanded Disability Status Scale, FCD = Focal Cortical Dysplasia, GBS = Guillain-Barré Syndrome, IVIG = Intravenous Immunoglobulin, MG = Myasthenia Gravis, MG-ADL = Myasthenia Gravis Activities of Daily Living, MMN = Multifocal Motor Neuropathy, MMS = Myasthenic Muscular Score, MRC-SS = Medical Research Council Sum Score, PLEX = Plasma Exchange, PPS = Postpolio Syndrome, QMGS = Quantitative Myasthenia Gravis Score, RCT = Randomized Controlled Trial, RRMS = Relapsing-Remitting Multiple Sclerosis, SCIG = Subcutaneous Immunoglobulin, SF-36 PCS1 = Short Form-36 Health Survey Physical Component Summary, SR/MA = Systematic Review with Meta-Analysis.

Table 9: Summary of Findings of Included Systematic Reviews without Meta-Analyses

Main Study Findings	Author's Conclusion
Gogou, 2017[21]	
"No clear superiority of the IVIG administration in children with encephalitis has been demonstrated by clinical trials that were identified in the literature."[21] page 632 **"**Awaiting well-designed randomized controlled trials with clear and objective clinical endpoints, the use of IVIG could be justified in cases of children with poor seizure control in whom other treatments have failed."[21] page 633 "With regards to myasthenia gravis, recent data confirm the safety and efficacy of IVIG as a first-line treatment option. However, there are studies showing that maintenance IVIG therapy in myasthenia gravis does not affect disease activity, and that plasmapheresis may have a more consistent response rate than IVIG in some pediatric settings."[21] page 634	"Given the observed lack in systematic studies on this topic, future research needs to include more prospective and randomized controlled trials. Challenges that researchers often encounter include low prevalence, severity and the emergent nature of specific neurologic disorders, as well as complexity in therapeutic approach in most of them. Emphasis should be given to the comparison of IVIG with other available treatment options so that superiority, inferiority or equivalence between them can be assessed. Furthermore, evaluation of clinical outcomes should be combined with the assessment of laboratory parameters, such as cytokines profile or other biomarkers of immune system function. In this way, a clearer pathophysiological background of IVIG effect on neurologic conditions can be established."[21]page 634 "On the other hand, future studies should also focus on a "cost-effective" analysis of the IVIG use in childhood. According to the literature, IVIG are traditionally considered as a high cost therapy. The result of such an analysis may be a determinant factor of a wider application of this treatment, especially when other equally effective therapies exist. This is of particular interest in children with chronic neurologic conditions, as these patients and their families are likely to receive a wide range of different services (inpatient care, social services). In this way, if the use of such services can be reduced by the use of IVIG, then some or all of the intervention costs could be offset."[21]page 635 ""Current literature data support a favorable effect of IVIG on neurologic disorders in childhood with autoimmunity consisting the key factor in most cases. Furthermore, according to the literature, IVIG is perceived to have a low frequency of side effects, whereas prolonged use of other products such as corticosteroids can lead to serious adverse events. Until now, most literature data show that the administration of IVIG can play an essential role in cases of resistant pediatric epilepsy. On the other hand, identified studies present heterogeneity in methodology, provide moderate to low level evidence and therefore, cannot develop a framework for a more systematic use of IVIG in additional neurologic disorders in children. Awaiting larger and well-designed studies, the administration of IVIG should be guided by the individual needs of each pediatric patient."[21] page 635

Main Study Findings	Author's Conclusion
Zeiler, 2017[22]	

Primary:
• Electrographic seizure control
  ○ 3 resolved
  ○ 1 failed to respond
  ○ 19 failed to improve
  ○ 11 improved
  ○ 1 burst suppression
Secondary:
• Patient outcome
  ○ 15 patients returned to baseline function
  ○ 2 patients with mild deficits
  ○ 7 patients with severe deficits
  ○ 5 patients died
• Adverse events
  ○ 1 study documented no adverse events, 23 discuss adverse events
	"Currently, the routine use of IVIG for adult RSE cannot be recommended at this time. At this moment, IVIG therapy for adult RSE should be considered experimental. There needs to be extensive prospective study of this drug, and other immunotherapies, for RSE prior to widespread implementation."[22] page 179
	
	"Oxford level 4, GRADE D evidence exists to suggest an unclear impact of IVIG therapy in adult RSE. Routine use of IVIG in adult RSE cannot be recommended at this time."[22] page 179

Gadian, 2017[23]	
"We conclude that it is likely that IVIG reduces time to return of function (level 2b, n=150), but does not improve maximal disability score (level 2b, n=76) [for GBS]."[23] page 137 "In summary, the evidence shows that a good response to initial treatment with IVIG occurred in 78% (n=59), corticosteroids in 70% (n=44), and plasma exchange in 14% (n=7) [for CIDP]"[23] page 137 "We conclude it is possible that first-line treatment with IVIG improves response in CIDP (level 4, n=59)."[23] page 138 "In summary, the evidence shows that IVIG, corticosteroids, and plasma exchange seem to be effective in the treatment of myasthenia gravis, although treatment with multiple therapies is commonly required. We conclude it is possible that IVIG improves response in myasthenia gravis (level 4, n=67)."[23] page 138 "We conclude it is possible that IVIG improves recovery in initial treatment of ADEM (level 4, n=66). There is insufficient evidence to support or refute the use of IVIG in	"We recommend that IVIG should be considered in GBS, to speed recovery (grade B). Plasma exchange should be considered before IVIG in ventilated patients with GBS (grade B)."[23] page 137 "We recommend that IVIG and corticosteroids may be considered in the initial management of CIDP to improve response (grade C)."[23] page 138 **"**We recommend that IVIG, corticosteroids, and plasma exchange may be considered in myasthenia gravis (grade C)."[23] page 138 "We recommend that IVIG and corticosteroids may be considered in ADEM to improve recovery (level C). Plasma exchange may be considered in severe cases (level C)."[23] page 138 "We recommend that IVIG or other immunomodulation may improve outcome in N-methyl-D-aspartate receptor antibody encephalitis (grade C)."[23] page 139 **"**We recommend that IVIG or tacrolimus may be considered in Rasmussen syndrome

Main Study Findings	Author's Conclusion
selected patients with neuromyelitis optica."[23] page 138 "We conclude it is possible that IVIG improves recovery in N-methyl-D-aspartate receptor antibody encephalitis (level 4, n=6). It is possible that early immunomodulation improves outcome (level 4, n=5)."[23] page 139 "We conclude it is possible that IVIG reduces or stops seizures in Rasmussen syndrome (level 4, n=27). It is likely that IVIG and tacrolimus are equally effective (level 2b, n=16)."[23] page 139 "We conclude it is possible that IVIG reduces mortality and cardiac function in acute encephalitis with myocarditis (level 2b, n=83). There is insufficient evidence to support or refute the use of IVIG in selected patients with enterovirus 71 encephalitis with pulmonary oedema, and limbic encephalitis."[23] page 139 "We conclude that it is likely that IVIG improves recovery in selected patients with paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (level 2). It is possible that IVIG temporarily reduces tics with caudate nucleus antibodies (level 4, n=7). It is likely that IVIG reduces symptoms in Sydenham chorea (level 2b, n=14) at 1 month."[23] page 140 "We conclude it is possible that IVIG improves recovery in OMS in conjunction with corticosteroids/ACTH (level 4, n=92), and that early escalation with addition of rituximab/ cyclophosphamide improves recovery (level 4, n=53)."[23] page 141 "We conclude that there is insufficient evidence to support or refute the use of IVIG in selected patients with refractory epilepsy, febrile infection-related epilepsy syndrome, and Landau–Kleffner syndrome."[23] page 141 "We conclude that there is insufficient evidence to support or refute the use of IVIG in autism and lymphocyte abnormalities. It is possible that IVIG reduces cataplexy in narcolepsy, although repeated courses are frequently required (level 4, n=8). In adults and children, it is possible that early immunomodulation is more effective (level 4, n=19)."[23] page 141 "We conclude there is insufficient evidence to support or refute the use of IVIG in adrenoleukodystrophy (level 4, n=6)."[23] page 141	to improve seizure control (grade C). Immunotherapy may be more effective before development of drug-resistant seizures (grade D)."[23] page 139 "We recommend that IVIG should be considered in acute encephalitis with myocarditis to improve mortality and cardiac function (grade C)."[23] page 139 "We recommend that IVIG should be considered in selected patients with a diagnosis of paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (grade B). IVIG may be considered in selected cases of Tourette syndrome (grade D). IVIG may be considered in more severe cases of Sydenham chorea (grade C)."[23] page 140 "We recommend that IVIG in conjunction with other immunomodulation may improve outcome in OMS (grade C)."[23] page 141 "We recommend that IVIG may be considered in narcolepsy to reduce cataplexy symptoms (grade C)."[23] page 141

Main Study Findings	Author's Conclusion
Gernigon, 2017[24]	
"IVIGs were found to be efficacious in randomized clinical trials (RCTs) or meta-analyses of RCTs, based on an overall level of evidence considered: • High for two indications (chronic inflammatory demyelinating polyneuropathy [CIDP] and Guillain-Barré syndrome); • Moderate for one indication (multifocal motor neuropathy); • Low for six indications (dermatomyositis, myasthenia gravis [exacerbation, crisis], polymyositis, remitting multiple sclerosis, stiff person syndrome, and Lambert-Eaton myasthenic syndrome)."[24] page xiv "The scientific data were considered insufficient for 14 indications: diabetic amyotrophy, acute disseminated encephalomyelitis (ADEM), autoimmune encephalitis, Rasmussen's encephalitis, the chronic form of myasthenia gravis, neuromyelitis optica, paraneoplastic neuropathy, IgM paraproteinemic neuropathy, intensive care polyneuropathy, primary-progressive multiple sclerosis, lateral amyotrophic sclerosis, opsomyoclonus syndrome, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), and autism spectrum disorder."[24] page xiv	IVIGs are recommended treatments for Myasthenia gravis, and Guillain-Barré syndrome (or its variants, such as Miller-Fisher syndrome) IVIGs are possible treatments for Dermatomyositis (including the juvenile form), Acute disseminated encephalomyelitis (ADEM), Rasmussen's encephalitis, Myasthenia gravis, Polymyositis (including immune-mediated necrotizing myopathies), Remitting multiple sclerosis, Stiff person syndrome, Lambert-Eaton myasthenic syndrome, and Opsomyoclonus syndrome IVIGs are not recommended treatments (due to inadequate efficacy, a lack of pathophysiological justification or their potentially harmful effect) for Adrenoleukodystrophy, Alzheimer's disease, Inclusion body myositis, IgM paraproteinemic neuropathy, Intensive care polyneuropathy, Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome, Primary- or secondary-progressive multiple sclerosis, Amyotrophic lateral sclerosis, Autism spectrum disorder Insufficient data for Diabetic amyotrophy, Autoimmune encephalitis, Neuromyelitis optica, Paraneoplastic neuropathy, PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)
Vitaliti, 2015[25]	
Sydenham's Chorea (SC)	"In Sydenham Chorea the use of methylprednisolone was found in most cases as efficient as IVIG."[25] page 2749
Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS)	"In the studies we analyzed IVIG were found to be efficient in the treatment of post-streptococcal neurodegenerative disorders, even if in PANDAS, plasma-exchange (PE) showed a higher efficiency."[25] page 2749
Tourette Syndrome (TS)	"[In] Tourette's Syndrome, Colecoxib was successfully used in one patient."[25] page 2749
Acute Disseminated Encephalomyelitis (ADEM)	"IVIG[s] were also successfully used in ADEM."[25] page 2749
Multiple Sclerosis (MS)	"Pediatric Multiple Sclerosis seems to respond better to immunosuppressant agents (Mitoxantrone, Cyclophosphamide, Natalizumab)."[25] page 2749

Main Study Findings	Author's Conclusion
Devic's Neuromyelitis Optica (NMO)	"[Neuromyelitis optica] seems to respond better to immunosuppressant agents … (Rituximab, Mycofenolate)."[25] page 2749
Guillan-Barré syndrome (GB)	"IVIG[s] were also successfully used in … Guillan-Barré syndrome."[25] page 2749
Overall	"Neurodegenerative disorders actually constitutes a clinical challenge for pediatrician both from a diagnostic and a therapeutic point of view, as their pathogenesis is still object of study, and immunotherapeutic approaches are not still standardized for pediatric age. While progress for adults in this therapeutic field has arisen from the development of biological drugs as targets to antigenic and immunological markers, the use of immunotherapy to treat neurodegenerative disorders has still not been standardized for children. Protocols also vary from one center to another, considering also that the most therapeutic attempts find their basis on adult studies."[25] page 2760

ADEM = Acute Disseminated Encephalomyelitis, CIDP = Chronic Inflammatory Demyelinating Polyradiculoneuropathy, GBS = Guillan-Barré Syndrome, MG = Myasthenia Gravis, MS = Multiple Sclerosis, NMO = Devic's Neuromyelitis Optica, OMS = Opsoclonus-Myoclonus Syndrome, PANDAS = Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections, POEMS = Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes, RCT = Randomized Controlled Trial, RSE = Refractory Status Epilepticus, SC = Sydenham's Chorea, SR = Systematic Review, TS = Tourette Syndrome.

Table 10: Summary of Findings of Included Randomized Controlled Trials

Main Study Findings	Author's Conclusion
Dodel, 2013[27]	

Primary endpoint:
• Median area under the curve of plasma concentration of $A\beta_{1–40}$ between the last infusion and the final visit
Secondary endpoints:
• Area under the curve for plasma concentration of $A\beta_{1–42}$ and of anti-Aβ autoantibodies
  ○ Lower in the infusion-every-two-weeks group between 0.4 grams intravenous immunoglobulin per kilograms bodyweight and placebo (p=0.0216)
  ○ No other significant comparisons (including pooled groups)
• Serious Adverse Events
  ○ 4 (10%) IVIG group
  ○ 4 (29%) Placebo group
• Non-Serious Adverse Events
  ○ 25 (60%) IVIG group
  ○ 9 (64%) Placebo group
	"Our study has limitations, despite careful design and execution. The small size of each treatment group with large variations in disease trajectories reduces the likelihood of recording clinically significant data favouring one dose over another. Extrapolation of our findings to other patient groups is limited by the small sample size in each group (especially in the placebo groups) and by the inclusion and exclusion criteria. Furthermore, patients were exposed to treatment for only 6 months, which prevents detection of a disease-modifying effect. Finally, as in other studies of anti-amyloid drugs, the disease course of Alzheimer's disease might have been too advanced in our study population to detect an effect. Intervention at an earlier disease stage might be more beneficial, particularly for clinical outcomes. Although different doses and intervals have been used in this [trial] … we cannot conclude whether higher or more frequent doses are needed. Lastly, we cannot rule out that intravenous immunoglobulin treatment might not be effective in patients with Alzheimer's disease."[27] page 242
	
	"In conclusion, this trial showed favourable safety and tolerability of intravenous immunoglobulin and the absence of severe autoimmune reactions. Longer studies of larger populations are needed to assess effects on cognition and function in patients with Alzheimer's disease."[27] page 242

van Klink, 2016[28]	
Primary endpoint: • No difference in neurodevelopmental impairment: 1 (3%) IVIG group versus 1 (3%) Placebo group (p=1.00) Secondary endpoints: • No difference in presence of allergies: 4 (12%) IVIG group versus 6 (19%) Placebo group (p=0.51) • No difference in susceptibility to ear, nose and throat infections: 7 (21%) IVIG group versus 9 (28%) Placebo group (p=0.48)	"The most important limitation of our study is the relatively incomplete follow-up. We were not able to examine 14 children (18%) due to the loss of contact address or the parents' decline to participate. However, a comparison of baseline characteristics between the study and the lost-to-follow-up group showed no significant differences, assuming little bias. Lastly, our randomized controlled study was designed to detect a difference in the short-term outcome (namely the use of ET in the neonatal period) and was not designed to detect a difference in the long-term neurodevelopmental outcome. Our conclusions may thus be limited by the relatively small sample size and power."[28] page 202 "We found no differences in long-term neurodevelopmental outcome in children with rhesus HDFN treated with IVIG compared to placebo. Standardized long-term follow-up studies with large enough case series and sufficient power are needed to replicate

Main Study Findings	Author's Conclusion
	these findings."[28] page 202
Absoud, 2017[29]	
"Of the 28 patients screened for eligibility, two were randomised into the study between 4 March 2015 and 8 February 2016, precluding any statistical analysis of the data, and, consequently, any differences in treatment outcomes between the two study arms could not be determined. However, we identified multiple barriers to accrual into the study. These included the strict inclusion criteria, the short enrolment window, challenges associated with the use of the ASIA Impairment Scale as the primary outcome measure, an inaccurate estimation of the incidence of TM and the spectrum of severity within the target population and the variability of research funding of individual sites."[29] page xx	"The clinical and health economic impacts of the use of IVIG in addition to standard therapy with IVMP in the treatment of adults and children with TM/NMO could not be determined in the study. As the study question is crucial to inform the acute treatment of TM/NMO patients, and thus one that necessitates further investigation, we recommend additional research to establish the incidence and the spectrum of severity of the disorder within the intended study population, alongside evaluating the utility of alternative primary outcome measures such as the ASIA motor score and other patient-derived outcome measures. The success of future intervention trials in TM will be contingent on being able to overcome recruitment barriers identified in this study, which may have broader implications for investigators embarking on similar studies in other rare disorders."[29] page xxi "Although the paucity of patient encounters and other operational barriers played a significant role in the study under-recruiting, the contributory effect of the study design (in terms of eligibility criteria) to the under-recruitment of the study cannot be overlooked. An analysis of site screening logs and feedback from investigators indicated that the exclusion of 'less severe' patients (i.e. patients with an ASIA impairment score of D) had some impact on the recruitment of patients into the study. Approximately 48% (n = 11/23) of screened patients who did not meet the eligibility criteria did not do so as a result of their symptoms being 'mild' or being assessed as having an ASIA impairment score of D. The study team recognised this trend while the study was still active and considered amending the protocol to allow the inclusion of patients assessed as having an ASIA impairment score of D or those whose symptoms were considered to be 'mild' at the time of presentation. However, the primary end point of the study required patients to have at least an ASIA impairment score of C to enable a two-grade improvement in this scale to be observed."[29] page 21 "The short window for recruitment (5 days from the date of first commencement of steroid therapy) was the second factor that contributed to the low recruitment rate. Although it would have been easy to remove this restriction, the early treatment paradigm was key to the study question and so was retained."[29] page 21

Main Study Findings	Author's Conclusion
Kile, 2017[30]	
Primary: • No significant difference in annualised per cent change in ventricular volume (APCV) as measured by MRI at baseline, 12 and 24 months following the first infusion of either 0.4 grams per kilogram body weight of IVIG or 0.9% saline solution every 14 days times 5 infusions between IVIG and placebo groups at 24 months Secondary: • No significant difference in change in cognitive performance between baseline, 12 and 24 months after the first infusion as measured by Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) between IVIG and placebo groups at 24 months • No significant difference in change in cognitive performance between baseline, 12 and 24 months after the first infusion as measured by Mini Mental State Examination (MMSE) between IVIG and placebo groups at 24 months • No significant difference in change in cognitive performance between baseline, 12 and 24 months after the first infusion as measured by CDR-Sum of Boxes (CDR-SB) between IVIG and placebo groups at 24 months	"There are limitations to this study. This study had a small sample size, which we attempted to mitigate by reducing variation among study participants by using a single site, the same MRI, consistent raters and examiners, and an objective primary end point to measure brain atrophy."[30] page 111 "In summary, these results provide limited evidence of a potential disease-modifying effect of IVIG during the MCI stage of AD in the form of reduced brain atrophy as well as reduced conversions to AD dementia at 1 year. This was an initial exploratory study aimed to provide insight for a potential treatment effect from IVIG in the early stages of this devastating disease. This study does not provide enough evidence for the clinical use of IVIG for MCI due to AD, but we hope this will help inform future investigations."[30] page 111
Barnett, 2013[31]	
Primary: • No significant change in Myasthenia Gravis Quality of Life 60-Item Version (MG-QOL-60) scores between baseline and 2 weeks after treatment between IVIG and placebo groups (p=0.52) • No significant change in Myasthenia Gravis Quality of Life 15-Item Version (MG-QOL-15) scores between baseline and 2 weeks after treatment between IVIG and placebo groups (p=0.41)	"One limitation of this study is that the scales used do not necessarily reflect the direct impact of each treatment on QOL. Another limitation is that the gold standard for clinical improvement in MG-QOL has not been defined. However, since both QOL scales have had validation studies done previously and were combined with objective outcome measures (ie, the QMGS) in the current study, it is probable that the results reflect a meaningful clinical improvement. An additional limitation is that our population sample of 62 patients was a subset of the total study population (84), but given that the demographic profile of the subset mirrored that of the total study population and that the subset is relatively large, provides confidence in the results."[31] page 96 "In conclusion, this study confirms that IVIG and PLEX are comparable immunomodulatory treatments for patients with worsening MG as measured by improvements in MG-QOL as well as by improvement in disease severity. Furthermore, the results of our study support the use of the MG-QOL-15 as an outcome measure in future clinical trials of MG aiming to assess QOL."[31] page 96

Main Study Findings	Author's Conclusion
Relkin, 2017[32]	
Primary: • No significant change in Cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) between baseline and every 3 months through month 18 between (0.2 and 0.4) IVIG groups and placebo • No significant change in Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL) between baseline, 9 months, and 18 months between (0.2 and 0.4) IVIG groups and placebo Secondary: • No significant change from baseline at 9 months in ADAS-Cog between (0.2 and 0.4) IVIG groups and placebo (p=0.237 and p=0.586, respectively) • No significant change from baseline at 9 months in ADCS-ADL between (0.2 and 0.4) IVIG groups and placebo (p=0.912 and p=0.878, respectively) • Change from baseline at 9 months in Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change (ADCS-CGIC) between (0.2 and 0.4) IVIG groups and placebo (p=0.766 and p=0.660, respectively) • Change from baseline at 9 months in Neuropsychiatric Inventory (NPI) between (0.2 and 0.4) IVIG groups and placebo (p=0.075 and p=0.640, respectively) • Change from baseline at 9 months in Quality of Life in Alzheimer's Disease Scale (QOL-AD) between (0.2 and 0.4) IVIG groups and placebo (p=0.094 and p=0.093, respectively)	"Participants with mild to moderate AD showed good tolerability of treatment with low-dose human IVIG for 18 months but did not show beneficial effects on cognition or function relative to participants who received placebo."[32] page 1768 "This study provides Class II evidence that IVIG infusions performed every 2 weeks do not improve cognition or function at 18 months in patients with mild to moderate AD."[32] page 1768
Alipour-Faz, 2017[33]	
• Duration of hospitalization stay ○ 20.27 ± 8.42 days IVIG group versus 21.08 ± 5.29 PLEX group (p=0.78) • Length of ICU stay after surgery ○ 2.33 ± 1.49 days IVIG group versus 3.75 ± 3.10 days PLEX group (p=0.16) • Length of intubation period ○ 2 (17%) IVIG group for a median of 0 versus 7 (58%) PLEX group for a median of 13 hours (p=0.01) • Duration of surgery ○ 3.46 ± 0.68 hours IVIG group versus 4.17 ± 1.03 hours PLEX group (p=0.05)	"We could not provide evidence for the secondary outcomes including survival rate and long-term side effects of interventions that are limitations of our study. Therefore, studies with a larger sample size and long-term follow up are recommended. In this study, we concluded that clinicians can consider IVIG in patients with indication of thymectomy as an alternative for the plasmapheresis method.[33] page 248 "Administration of immunomodulation is one of the effective managements in patients with myasthenia gravis. Plasmapheresis or IVIG could be particularly used for preparation before thymectomy. Both the methods are similar in the case management of these patients. However, IVIG is more appropriate and cost-effective than plasma exchange."[33] page 248

Main Study Findings	Author's Conclusion
• Dose of steroid administered ○ 30.63 ± 12.08 milligrams IVIG group versus 39.00 ± 15.05 milligrams PLEX (p=0.22)	
Jann, 2012[34]	
Primary: • Lower pain intensity using Visual Analog Scale (VAS) in IVIG group versus control group (no pain reduction) (p<0.01) • Lower pain intensity using Short Form McGill Pain Questionnaire (SF-MPQ) in IVIG group versus control group (no pain reduction) (p<0.01) Secondary: • Higher Quality of life (QOL) using the Short Form 36 (SF-36) questionnaire in IVIG group versus control group (p<0.01) • Higher Quality of life (QOL) using the Clinical Global Impression of Change (CGI-C) in IVIG group versus control group (p<0.01) • Higher Quality of life (QOL) using the Patient Global Impression of Change (PGI-C) in IVIG group versus control group (p<0.01) • 1 adverse event in the IVIG group reported a hypertensive peak event 4 days after treatment, but it was not considered related to the treatment as the patient has a previous history of such episodes	"[S]everal limitations should be considered when interpreting study results. Firstly, this was a no-placebo, open study and neither the investigators nor patients were blinded and therefore resulted in favoring better outcomes evaluation in the IVIG-treated patient group. Patients in the IVIG group would have a positive attitude toward the new treatment and, similarly, a potential negative attitude of patients being randomized to no intervention at all might be possible. Both attitudes were a potential source of bias. For instance, it should be noted both the near absence of any pain relief in the control group, which is in contrast with a recent report, and the apparent high percentage of responders in comparison with other reports. The unblinded nature of our study and its associated influence on the attitude of patients could explain these supposed discrepancies. The second limitation is related to generalization of results. As it was a limited cohort study, results can not be generalized to all individuals with refractory neuropathic pain. The wide group of pathologies with associated neuropathic pain in our sample of patients partially helped to reduce this limitation. Another possible criticism is that the two arms of this study are not matched for the peripheral nerve disease. It was not done because the aim of the study was to reduce neuropathic pain and not to treat painful neuropathies. The original idea was that IVIG can be a symptomatic therapy and not only a disease-modifying treatment. Lastly, our follow-up period was 8 weeks, which only allowed short-term outcome assessments."[34] pages 1339-1340 "In summary, although definitive conclusions cannot be drawn because of the pilot nature of this study, IVIG had a significant beneficial impact on neuropathic pain severity in patients resistant to conventional treatments. Moreover, patients significantly improved their quality of life. Significant side effects were not observed along the follow-up."[34] page 1340

AD = Alzheimer's disease, ADAS-Cog = Cognitive subscale of the Alzheimer's Disease Assessment Scale, ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Scale, ADCS-CGIC = Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change, CGI-C = Clinical Global Impression of Change, ICU = Intensive Care Unit, IVIG = Intravenous Immunoglobulin, IVMP = intravenous methylprednisolone, MG = Myasthenia Gravis, MG-QOL-60 = Myasthenia Gravis Quality of Life 60-Item Version, MG-QOL-15 = Myasthenia Gravis Quality of Life 15-Item Version, MRI = Magnetic Resonance Imaging, NMO = Neuromyelitis Optica, NPI = Neuropsychiatric Inventory, PGI-C = Patient Global Impression of Change, PLEX = Plasma Exchanges, QOL = Quality of Life, QOL-AD = Quality of Life in Alzheimer's Disease Scale, RCT = Randomized Controlled Trial, SF-36 = Short Form 36 quality of life questionnaire, SF-MPQ = Short Form McGill Pain Questionnaire, TM = Transverse Myelitis, VAS = Visual Analog Scale.