Treatment for postpolio syndrome (Review)

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[Intervention Review]

Treatment for postpolio syndrome

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ABSTRACT

Background

Postpolio syndrome (PPS) may affect survivors of paralytic poliomyelitis and is characterised by a complex of neuromuscular symptoms leading to a decline in physical functioning. The effectiveness of pharmacological treatment and rehabilitation management in PPS is not yet established.

Objectives

To review systematically the effects of any treatment for PPS compared to placebo, usual care or no treatment.

Search strategy

We searched the following databases on 1 October 2010: Cochrane Neuromuscular Disease Group Specialized Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycINFO and CINAHL Plus from inception to September 2010.

Selection criteria

Randomised and quasi-randomised trials of any form of pharmacological or non-pharmacological treatment for people with PPS. The primary outcome was self-perceived activity limitations and secondary outcomes were muscle strength, muscle endurance, fatigue, pain and adverse events.

Data collection and analysis

Two authors independently selected eligible studies, assessed risk of bias and extracted data.

Main results

Nine pharmacological (modafinil, intravenous immunoglobulin, pyridostigmine, lamotrigine, amantadine, prednisone) and three non-pharmacological (muscle strengthening, rehabilitation in a warm climate (i.e. temperature ± 25°C, dry and sunny) and a cold climate (i.e. temperature ± 0°C, rainy or snowy), static magnetic fields) studies were included in this review. None of the included studies was completely free from any risk of bias and the most prevalent risk of bias was lack of blinding.

There is moderate quality evidence that intravenous immunoglobulin has no beneficial effect on activity limitations and there is inconsistency in the evidence for effectiveness on muscle strength and pain. Results of one trial provide very low quality evidence that lamotrigine might be effective in reducing pain and fatigue, resulting in fewer activity limitations. Data from two single trials suggest

that muscle strengthening of thumb muscles (very low quality evidence) and static magnetic fields (moderate quality evidence) are beneficial for improving muscle strength and pain, respectively, with unknown effects on activity limitations. Finally, there is evidence varying from very low quality to high quality that modafinil, pyridostigmine, amantadine, prednisone and rehabilitation in a warm or cold climate are not beneficial in PPS.

Authors' conclusions

Due to insufficient good quality data and lack of randomised studies it is impossible to draw definite conclusions on the effectiveness of interventions for PPS. Results indicate that IVIG, lamotrigine, muscle strengthening exercises and static magnetic fields may be beneficial but need further investigation.

PLAIN LANGUAGE SUMMARY

Treatment for postpolio syndrome

Postpolio syndrome (PPS) is a condition that can affect polio survivors years after recovery from an initial paralytic attack by the polio virus. PPS is characterised by progressive or new muscle weakness or decreased muscle endurance in muscles that were previously affected by the polio infection and in muscles that seemingly were unaffected, generalised fatigue and pain. These symptoms often lead to a decline in physical functioning.This review found inadequate evidence from randomised controlled studies to make definite conclusions on the effectiveness of different treatment options in people with PPS. Results indicate that drugs like IVIG and lamotrigine or muscle strengthening and static magnetic fields may be beneficial but need further investigation.

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

Modafinil versus placebo for postpolio syndrome

Patient or population: patients with postpolio syndrome
Settings:
Intervention: Modafinil versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Modafinil versus placebo				
Activity limitations post-treatment Measured with the SF-36 PF[1]. Scale from: 0 to 100. Follow-up: 6 weeks	The mean activity limitations post-treatment in the control groups was **37.28** [2]	The mean Activity limitations post-treatment in the intervention groups was **1.28 higher** (3.56 lower to 6.12 higher)		33 (1 study[3])	⊕⊕⊕⊕ **high**	
Adverse events	See comment	See comment	Not estimable	50 (2 studies)	See comment	See additional table 1

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] SF-36 PF: Short Form-36 Health Survey Physical Functioning scale. Higher scores represent fewer activity limitations.

[2] The control group received placebo.
[3] Cross-over study in which 36 patients were randomised, 33 completed required interventions.

BACKGROUND

Postpolio syndrome (PPS) is a complex of neuromuscular symptoms that occurs in many survivors of paralytic polio, usually 15 years or more after the acute illness. It is characterised by a gradual or, in rare cases, a sudden onset of progressive and persistent new muscle weakness or decreased muscle endurance, with or without generalised fatigue, muscle atrophy, or muscle and joint pain (March of Dimes Foundation 2000). Since there are no specific diagnostic tests for PPS, diagnosis is based on exclusion of other possible causes for the new symptoms.

In Western countries, the large poliomyelitis epidemics occurred in the 1940s and 1950s. Therefore, many polio survivors are now experiencing the late effects of polio. The total number of polio survivors is estimated at 20 million by the World Health Organization. The prevalence of PPS has been reported to range from 15% to 80% of all people with previous paralytic polio depending on the criteria applied and population studied (Farbu 2006). Although polio epidemics have more or less disappeared in Western countries thanks to the widespread use of polio vaccines, the continuing prevalence of polio in developing countries means that PPS will continue to be a problem for many decades to come.

PPS is regarded to be a slowly progressive condition. In a recent systematic review researchers found that, among long-term studies, the deterioration in muscle strength varied from 7% in four years to 15% in eight years (Stolwijk-Swuste 2005). The decline in muscle mass leads to a decline in physical functioning as the reduced muscle capacity falls short to meet the demands of daily physical activities (Nollet 2003a). Furthermore, fatigue and pain are commonly reported problems by people with PPS (Nollet 1999) and these may also have a negative impact on physical functioning.

The pathogenesis of PPS is still unclear and is probably multifactorial. The most widely accepted assumption is that the motor units, which are enlarged due to reinnervation in response to denervation as a result of acute poliomyelitis, do not remain stable throughout life (Wiechers 1981; Wiechers 1988). There is distal degeneration of axons possibly because of persistent high metabolic stress. The initial balance between denervation and reinnervation of muscle fibres becomes disrupted and when denervation predominates, progressive muscle weakness occurs. This concept has been supported by the finding of single atrophic muscle fibres in muscle biopsy studies and signs of acute denervation on electromyography (Dalakas 1988; Einarsson 1990; Grimby 1989). Other supposed explanations for the pathogenesis of PPS include virus persistence (Jubelt 1995) and immunological factors (Ginsberg 1989). Factors that may contribute to the symptoms of PPS are neuromuscular transmission defects (Trojan 1993) and an impaired ability to activate muscles (Allen 1994; Beelen 2003).

Treatment for PPS

The potential arsenal of treatment options for PPS may be divided into pharmacological and non-pharmacological interventions.

Pharmacological interventions

Pharmacological treatments vary in terms of their respective points of action and targeted effects. Amantadine, bromocriptine and modafinil act on different regions of the brain and are intended to address generalised fatigue in PPS (Bruno 1996; Chan 2006; Dunn 1991; Stein 1995; Vasconcelos 2007). Insulin-like growth factor (IGF-I) and human growth hormone, which stimulates the secretion of IGF-I, may be suitable agents for the treatment of PPS. IGF-I is thought to enhance regeneration of peripheral nerves by axonal sprouting which in turn positively influences muscle strength (Gupta 1994; Miller 1997; Shetty 1995). High-dose prednisone and intravenous immunoglobulin (IVIG) were studied to determine whether their immunosuppressive or immunomodulating effects might have a beneficial effect on muscle strength, fatigue and pain (Dinsmore 1995; Farbu 2007; Gonzalez 2006). Pyridostigmine is a cholinesterase inhibitor, thus prolonging the survival of acetylcholine in the neuromuscular synapse. Several studies investigated its effects on fatigue and other symptoms of PPS (Horemans 2003; Seizert 1994; Trojan 1995; Trojan 1999). Lamotrigine, a glutamate release blocker, was studied to evaluate whether the neuroprotective effect of the drug reduces fatigue and pain in PPS (On 2005). Coenzyme Q10 and selegiline were evaluated for their effects on muscle metabolism and muscle strength respectively, and the effect on PPS symptoms in general (Bamford 1993; Mizuno 1997).

Non-pharmacological interventions

Since no curative treatment is available for PPS, rehabilitation management is considered the mainstay of treatment. The aim is to reach a functional balance by increasing capacities and reducing demands. Several different approaches can be applied.
Strength training and aerobic exercise may increase functional capacities in patients with PPS (Agre 1997; Chan 2003; Einarsson 1991; Ernstoff 1996; Jones 1989; Kriz 1992; Spector 1996). However, the information available in the literature is contradictory. On the one hand, PPS patients are advised to avoid muscular overuse and intensive training as this could worsen muscle weakness and fatigue and provoke a further loss of muscular strength (Farbu 2006). On the other hand, physically active PPS patients were found to have fewer symptoms and a higher functional level than inactive patients (Rekand 2004). Exercise in water may be beneficial because it minimises biomechanical stress on muscle and joints (Willen 2001). Training in a warm, dry and sunny climate may have beneficial effects on several physical, psychological and social dimensions of health in PPS (Strumse 2003). For PPS patients with respiratory impairment, respiratory muscle training may be useful to enhance respiratory muscle endurance and improve well-being (Klefbeck 2000).

Proper orthoses and assistive devices such as crutches, wheelchairs, motorised scooters and home adaptations may facilitate daily life activities. For example, lightweight carbon orthoses may have a beneficial effect on the energy cost of walking and walking ability (Brehm 2007; Heim 1997).

Lifestyle changes including pacing of activities, taking rest intervals and reducing weight have been proposed to relieve symptoms of PPS. People with PPS have often learned to disregard or mask their symptoms in order to achieve an active life. Therefore, they might have great difficulty with adapting their lifestyle to their decreasing abilities and psychological support might be indicated (Nollet 2003). Effectiveness of lifestyle modification in alleviating shoulder overuse symptoms has been investigated (Klein 2002) and collaborative educational sessions are proposed as a major component of a comprehensive rehabilitation program (Davidson 2008).

Although the European Federation of Neurological Societies (EFNS) task force performed an extensive evaluation of existing evidence for the clinical effectiveness of therapeutic interventions for PPS, no systematic review on this topic has been performed (Farbu 2006). Therefore, we have systematically reviewed the evidence from randomised or quasi-randomised controlled trials of treatment for PPS. This review provides guidance for daily practice in the treatment of PPS for rehabilitation physicians and neurologists. Furthermore, it provides a basis for researchers to initiate novel trials of interventions in PPS.

OBJECTIVES

The objective was to review systematically the evidence from randomised and quasi-randomised controlled trials for the effect of any pharmacological or non-pharmacological treatment for PPS compared to placebo, usual care or no treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) and quasi-randomised trials of any treatment for people with PPS.

Types of participants

We included studies on participants with a diagnosis of PPS. Essential criteria to the diagnosis were:

1. a history of paralytic poliomyelitis;
2. a period of partial or complete functional recovery after acute poliomyelitis, followed by an interval of stable neurologic function;
3. new or increased neuromuscular symptoms.

We did not include experimental data from animal models.

Types of interventions

We included any form of pharmacological or non-pharmacological treatment. Drugs may include cholinesterase inhibitors (pyridostigmine), steroids (prednisone or prednisolone), intravenous immunoglobulin, dopamine-2 receptor agonists (bromocriptine), glutamate release blockers (lamotrigine), human growth hormone, IGF-I, amantadine, modafinil, coenzyme Q10 and selegiline. Non-pharmacological treatment may include physical treatment (e.g. aerobic exercise, muscle strengthening exercise, respiratory muscle training, warm climate training, hydro training), orthoses and other assistive devices, respiratory support, lifestyle change, weight control or surgical intervention. We also included studies that examined combinations of these treatments. We compared interventions against placebo, usual care or no treatment.

Types of outcome measures

The primary outcome measure was self-perceived activity limitations. We accepted any scale that measured this concept, such as the physical functioning scale of the Short Form-36 Health Survey (SF-36 PF) and the physical mobility category of the Nottingham Health Profile (NHP-PM).

The secondary outcome measures were:

1. muscle strength;
2. muscle endurance;
3. fatigue;
4. pain;
5. adverse events subdivided into minor adverse events and serious adverse events (resulting in cessation of treatment, requiring hospitalisation or being life-threatening or fatal).

For the secondary measures, we also accepted any scale that measured these concepts. We used standardised mean differences to make comparisons. Alternatively, participants may have been dichotomised into no change or improved and worse; if this was the case we used the numbers unchanged or improved and the numbers which were worse and calculated risk ratios. Outcomes were evaluated directly post-treatment. When interventions were expected to have long-term effects, we also evaluated long-term outcomes (greater than 12 weeks following treatment). If a study did not report change from baseline scores, but final scores were available, these data were used for the analyses. The cost-effectiveness of treatments were considered in the Discussion provided there was information available.

Search methods for identification of studies

Search strategies were developed in consultation with the Cochrane Neuromuscular Disease Group Trials Search Co-ordinator.

Electronic searches

We searched for relevant trials using the following databases:

- Cochrane Neuromuscular Disease Group Specialized Register (1 October 2010)
- Cochrane Central Register of Controlled Trials (CENTRAL, Issue 3, 2010 in *The Cochrane Library*)
- MEDLINE (January 1966 to September 2010)
- EMBASE (January 1947 to September 2010)
- PsycINFO (January 1806 to September 2010)
- CINAHL Plus (January 1937 to September 2010)

The review search strategies for the different databases are shown in: Appendix 1 (CENTRAL); Appendix 2 (MEDLINE); Appendix 3 (EMBASE); Appendix 4 (PSYCHINFO); and Appendix 5 (CINAHL).

Searching other resources

In an effort to identify further published, unpublished and ongoing trials, we:

1. checked reference lists of all relevant articles;
2. searched databases of ongoing trials (Appendix 6) including:
    - Australian New Zealand Clinical Trials Registry (www.anzctr.org.au)
    - U.S. National Institutes of Health (www.clinicaltrials.gov)
    - International Standard Randomised Controlled Trial Number Register (www.ISRCTN.org)
    - UMIN-Clinical Trials Registry (www.umin.ac.jp/ctr/index/htm)
    - Dutch Trial Register (www.trialregister.nl)
3. contacted investigators known to be involved in research in this area.

Data collection and analysis

Selection of studies

Two review authors (FK, KU) independently screened the search results based on titles, keywords and abstracts and they read the full text of eligible studies identified in this way. The two authors decided on the suitability for inclusion in the review using pre-specified inclusion criteria. Disagreements were resolved by a consensus procedure, if necessary, with a third review author (NG). Authors were not blinded to the journals of publication, authors' names and institutional affiliation.

Data extraction and management

Two review authors (FK, KU) extracted the data independently onto a specially designed data extraction form. They wrote to study authors for further information when necessary. Disagreements were resolved with a consensus procedure, if necessary, with a third review author (NG). One author entered data into Review Manager 5 software (RevMan 5, RevMan 2008) and a second author independently checked the data entry.

Assessment of risk of bias in included studies

The two authors independently assessed all included studies for their risk of bias according to the guidance in the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2008). We assessed randomisation sequence generation, allocation concealment, blinding (participants, administrators of the intervention, and outcome assessors), incomplete outcome data (missing outcome data and intention-to-treat (ITT) analysis), selective outcome reporting and other sources of bias. We then made a judgement on each of these domains relating to the risk of bias, such that a judgement of 'yes' indicated a low risk of bias, 'no' a high risk of bias and 'unclear' unclear or unknown risk of bias. For two domains we further specified the original criteria of the Cochrane Handbook. In order to score a 'yes' for the blinding domain, blinding had to be ensured for all outcome measures, including patient-reported outcomes. In order to score a 'yes' for the ITT-analysis domain all participants had to be analysed in the groups they were randomised to irrespective of non-compliance and co-interventions. This did not apply to the missing values.

Measures of treatment effect

We summarised continuous data with mean differences (MD). If studies used different outcome measurements that addressed the same clinical outcome, standardised mean differences (SMD) were used. We summarised dichotomous data using risk ratios (RR). We expressed uncertainty with 95% confidence intervals (CIs).

Unit of analysis issues

We included cluster randomised trials if the appropriate data were reported to adjust for the design effect.

Dealing with missing data

The review authors wrote to trial authors to try to obtain any missing data. All analyses were performed in accordance with the ITT method, which includes all randomised participants regardless of loss to follow-up.

Assessment of heterogeneity

We explored statistical heterogeneity among results of different studies using the Chi^2 test with significance set at $P < 0.1$. We measured the percentage of variation between trial results due to heterogeneity rather than chance using the I^2 statistic, with a value greater than 50% indicating substantial heterogeneity.

Assessment of reporting biases

If meta-analysis was possible, we assessed publication bias using a funnel plot. We identified and reported on any selective reporting in the included trials, although we are aware that this method is not a reliable indicator of publication bias and any interpretations made on the basis of it should be made with great caution.

Data synthesis

We did not combine data from studies with different interventions. If there was more than one trial with a specific treatment and comparable outcome measures, we calculated a pooled estimate of the treatment effect across the trials using RevMan 5. We used a fixed-effect model to combine individual results if there was no significant heterogeneity among the included trials; otherwise, we used a random-effects model.

Subgroup analysis and investigation of heterogeneity

If the data were available, we performed subgroup analyses to explore possible sources of clinical heterogeneity with regard to treatment. Relationships between intervention effect and dose, treatment intensity or treatment duration were investigated. We were cautious about drawing conclusions if the results of the subgroup analyses were only based on between-study differences.

Sensitivity analysis

If possible, we performed sensitivity analyses by:

1. repeating the meta-analyses after omitting the trials in which a possible risk of bias was identified;
2. repeating the meta-analyses after omitting the trials that did not use the recent criteria for PPS defined by the March of Dimes (March of Dimes Foundation 2000).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

See Characteristics of included studies; Characteristics of excluded studies; and Characteristics of ongoing studies.

Results of the search

Search results from the Cochrane Neuromuscular Disease Group Specialized Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycINFO and CINAHL PLUS revealed 26, 29, 168, 459, 101 and 127 papers, respectively. The total number of references after deduplication was 717. Authors FK and KU screened the titles, keywords and abstracts of these search results and selected 26 citations of full-length articles and abstracts describing 23 studies. Additionally, the searches in the trial registers identified one ongoing study (see Characteristics of ongoing studies). The other searches did not add any further potentially eligible references.

Included studies

Twelve studies fulfilled the selection criteria and were included in this review. Nine studies evaluated pharmacological treatment in PPS: two studies on modafinil (Chan 2006; Vasconcelos 2007), two studies on intravenous immunoglobulin (IVIG) (Farbu 2007; Gonzalez 2006), two studies on pyridostigmine (Horemans 2003; Trojan 1999), and three single studies that evaluated lamotrigine (On 2005), amantadine (Stein 1995), and high-dose prednisone (Dinsmore 1995). There were two non-pharmacological studies evaluating the effect of physical treatment: one study comparing the effect of muscle strengthening of the thumb muscles with no training (Chan 2003) and one three-arm study comparing rehabilitation in warm climate (i.e. temperature ± 25°C, dry and sunny) versus rehabilitation in cold climate (i.e. temperature ± 0°C, rainy or snowy) versus usual care (Strumse 2003). There was one non-pharmacological study evaluating the effect of static magnetic fields (Vallbona 1997). The pharmacological treatment studies and the magnetic fields study were placebo-controlled studies with a parallel group design, except the two modafinil studies used a cross-over design and the lamotrigine study was classified as an open-label study. Because PPS is considered a reasonably stable chronic condition and modafinil is a drug with a temporary effect, we considered the use of a cross-over design appropriate in the two modafinil trials. Both physical treatment studies were classified as non-placebo-controlled studies with a parallel group design. Four studies (Farbu 2007; Gonzalez 2006; On 2005; Strumse 2003) included patients with PPS based on one of the definitions of Halstead (Halstead 1985; Halstead 1987; Halstead 1991), one study (Vallbona 1997) used the criteria of Dalakas (Dalakas 1995), one study (Horemans 2003) used the criteria of Borg (Borg 1996) and one study (Vasconcelos 2007) used the criteria of the March of Dimes (March of Dimes Foundation 2000). Five studies (Chan 2003; Chan 2006; Dinsmore 1995; Stein 1995; Trojan 1999) did not refer to any of these definitions but designed their own criteria. We contacted the authors of these five latter studies and they confirmed that their criteria met our pre-specified criteria.

Excluded studies

Eleven studies were excluded from this review. One study, evaluating the effect of recombinant insulin-like growth factor against placebo (Miller 1997), was excluded because the results were only published in an abstract. Three studies were excluded because they could not be classified as a RCT or quasi-randomised trial according to the definitions described in the Cochrane Handbook of Systematic Reviews of Interventions (Lefebre 2008). The first study evaluated the effect of bromocriptine in five patients with post-polio fatigue, after these patients had received placebo treatment for four weeks (Bruno 1996). The second study evaluated the effects of an aerobic walking program in two patients as compared to the results of a control patient who was not available for participation in the program (Dean 1988). The third study evaluated the effect of dynamic water exercise in 15 patients with PPS as compared to 13 patients who were unable to participate in the training program for practical reasons (Willen 2001). Three studies did not use a control group consisting of placebo, usual care or other treatment and were therefore excluded. The first study was a three-arm study investigating the effects of a home-based exercise program versus lifestyle modification versus the combination of these two interventions (Klein 2002). The second study compared the effects of a hospital-based exercise program with a home-based exercise program (Oncu 2009). The third study evaluated the effects of oral supplementation with coenzyme Q10 as add-on to resistance training against the effect of a placebo and resistance training (Skough 2008). Two studies, both evaluating the effect of aerobic training, did not include any of our pre-specified outcome measures (Dean 1991; Jones 1989). Finally, two studies were excluded because they did not meet our criteria for the diagnosis of PPS. The first study evaluated the effect of upper extremity aerobic training against no treatment (Kriz 1992). The second study is a three-arm study evaluating the effect of an online fatigue self-management program versus information-only versus no intervention in patients with chronic neurological conditions, including PPS (Ghahari 2010).

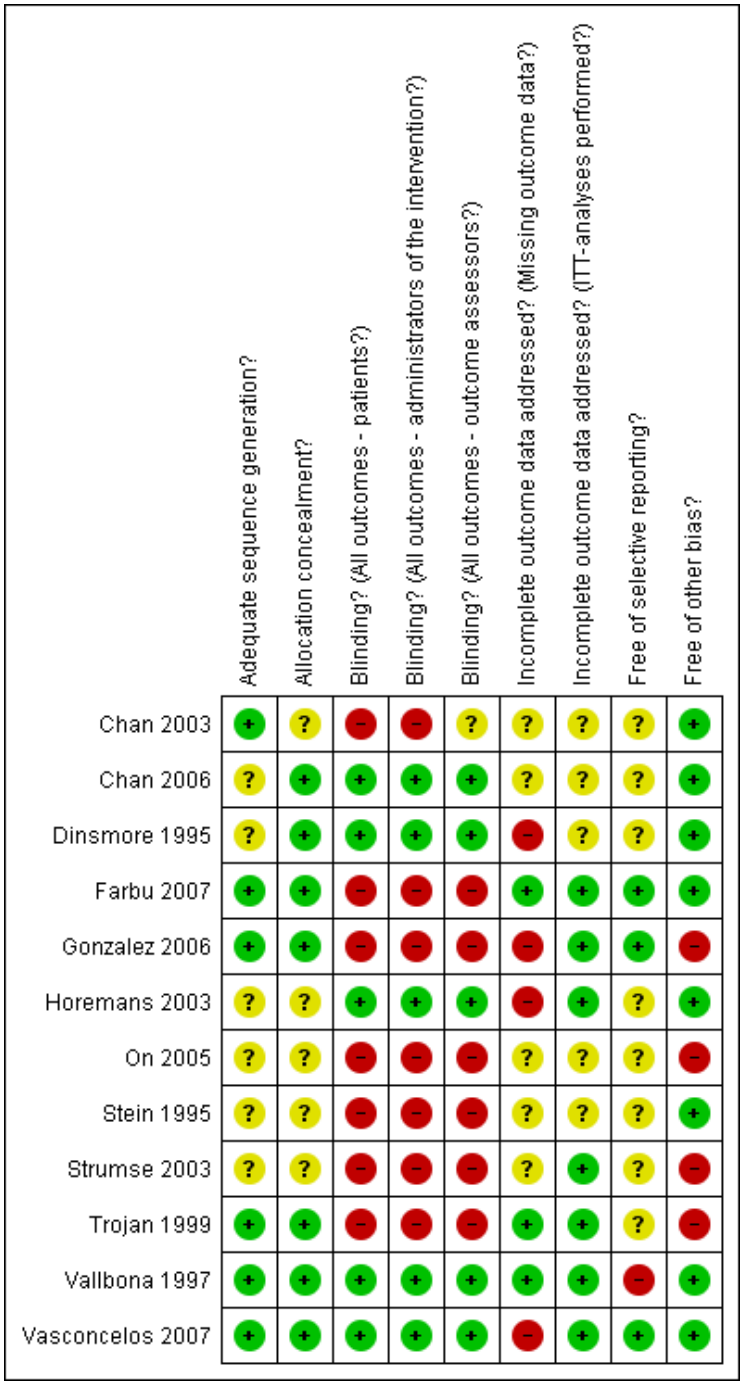
Ongoing studies

There is one ongoing study. This study is a three-arm study comparing the effects of exercise therapy versus cognitive behavioural therapy versus usual care (Koopman 2010). When results of this trial are published, it will be included in the next update of the review.

Risk of bias in included studies

See Characteristics of included studies and Figure 1.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



The method of randomisation sequence generation was adequate in half of the studies and unclear in the other half of the studies. Allocation concealment was adequate in seven studies and unclear in five studies. Blinding of patients, of administrators of the interventions and of outcome assessors was adequate in only five of the included trials (Chan 2006; Dinsmore 1995; Horemans 2003; Vallbona 1997; Vasconcelos 2007). In the two studies on physical treatment (Chan 2003; Strumse 2003) and the open-label study with lamotrigine (On 2005), patients and administrators of the interventions were aware of the treatment being given and therefore these studies are graded as inadequate on these items. Four pharmacological treatment studies (Farbu 2007; Gonzalez 2006; Stein 1995; Trojan 1999) did blind their patients and administrators of the interventions, but were graded as inadequate because side effects of the treatment could have caused unblinding. Since most of the studies included patient-reported outcomes, grading of blinding status for outcome assessors in these studies was dependent on the blinding status of the patient. Four studies (Dinsmore 1995; Gonzalez 2006; Horemans 2003; Vasconcelos 2007) had withdrawal of patients because of reasons related to the treatment and were therefore graded at a high risk of bias on the domain of 'missing outcome data'. Seven studies met our pre-specified criteria for the ITT-analysis domain (Farbu 2007; Gonzalez 2006; Horemans 2003; Strumse 2003; Trojan 1999; Vallbona 1997; Vasconcelos 2007). From three studies (Farbu 2007; Gonzalez 2006; Vasconcelos 2007), a study protocol was available, which were all published in trial registers. All pre-specified outcomes in these study protocols had been reported in the trial articles, so they were rated adequate on the domain of selective outcome reporting. Four studies (Gonzalez 2006; On 2005; Strumse 2003; Trojan 1999) were rated as negative on the domain 'other bias', as a result of baseline imbalances between groups. In conclusion, none of the included studies were completely free from any risk of bias and the most prevalent risk of bias was lack of blinding.

Effects of interventions

See: **Summary of findings for the main comparison** Modafinil versus placebo for postpolio syndrome; **Summary of findings 2** IVIG versus placebo for postpolio syndrome; **Summary of findings 3** Pyridostigmine versus placebo for postpolio syndrome; **Summary of findings 4** Lamotrigine versus control for postpolio syndrome; **Summary of findings 5** Amantadine versus placebo for postpolio syndrome; **Summary of findings 6** Prednisone versus placebo for postpolio syndrome; **Summary of findings 7** Muscle strengthening versus control for postpolio syndrome; **Summary of findings 8** Rehabilitation in cold climate versus usual care for postpolio syndrome; **Summary of findings 9** Rehabilitation in warm climate versus usual care for postpolio syndrome; **Summary of findings 10** Static magnetic fields versus placebo for postpolio syndrome

Results are given for each intervention separately in relation to predefined outcome measures. Adverse events for the pharmacological interventions are given in Table 1: 'Adverse events for pharmacological interventions'.

Table 1. Adverse events for pharmacological interventions

Study	Intervention	Serious adverse events	Minor adverse events
Chan 2006	Modafinil max 2 x 200 mg/day	None reported	Medication: anxiety and dry mouth (60%) Placebo: none reported
Vasconcelos 2007	Modafinil 2 x 200 mg/day	Medication: 3 patients (8%) (1. newly diagnosed endometrial cancer, 2. acute psychosis, 3. nervousness) Placebo: none reported	Medication: insomnia (11%), nervousness (11%), dry mouth (8%) , palpitation (5%), flushing (3%), abdominal discomfort (8%), urine change (11%), appetite loss (5%), upper respiratory problems (14%) Placebo: cold virus (6%), heartburn (6%), insomnia (3%), sinusitis (6%), diarrhoea (3%), dry eyes (6%) , joint or back pain (6%), headache (3%)

Table 1. Adverse events for pharmacological interventions (*Continued*)

Farbu 2007	IVIG 2g/kg body weight, 1 infusion	Medication: flu-like illness and chest myalgia (10%) Placebo: none reported	Medication: chills and/or fever (70%) Placebo: chills and/or fever (10%)
Gonzalez 2006	IVIG 90 g, 1 infusion repeated after 3 months	Medication: 1 patient (1%) developed a serious adverse event (not further specified) Placebo: 2 patients (3%) developed serious adverse events (not further specified)	Medication: gastrointestinal disorders (22%), general disorders and administration site conditions (19%), nervous system disorders (59%), skin and subcutaneous tissue disorders (37%) Placebo: gastrointestinal disorders (3%), general disorders and administration site conditions (9%), nervous system disorders (19%), skin and subcutaneous tissue disorders (7%)
Trojan 1999	Pyridostigmine 3 x 60 mg/day	Medication: 5 patients (8%) (1. palpitations and dizziness due to benign supraventricular arrhythmia, persisted after discontinuation of treatment, 2. sepsis secondary to severe diverticulitis, 3. infiltrating ductal carcinoma of breast, 4. painful muscle and gastrointestinal cramp and 5. nausea, diarrhoea, vomiting and faintness) Placebo: 1 patient (2%) angina, shortness of breath	Medication: 7 patients (11%) muscle cramps, abdominal pain, nausea, diarrhoea, profuse sweating, chest pain, fractured fibula, fractured rib, herpes zoster Placebo: 2 patients (3%) feeling drugged, blurred vision, nausea, diarrhoea
Horemans 2003	Pyridostigmine 4 x 60 mg/day	Medication: 1 patient (3%) severe diarrhoea Placebo: none reported	None reported
On 2005;	Lamotrigine 50 to 100 mg/day	None reported	None reported
Stein 1995	Amantadine 2 x 100 mg/day	None reported	Medication: insomnia (73%), dry mouth (9%) Placebo: none reported
Dinsmore 1995	Prednisone 80 mg/day continued by a 20 weeks dose reduction schedule	Medication: 2 patients (22%)(1. severe depression and 2. transient ischaemic attack, hypertension and dyspnoea on exertion) Placebo: 1 patient (13%) increasing weakness, acne, fungal infection and insomnia	Medication: 5 patients (56%) cataract, tinnitus, weakness, depression, acne, low back pain, irritability, hoarseness, blurred vision, urinary frequency, anxiety, fungal infection, sensitive gingiva and breasts. Placebo: 4 patients (50%) insomnia,

Table 1. Adverse events for pharmacological interventions (*Continued*)

			irritability, nausea.

Modafinil

Because both studies on modafinil (Chan 2006; Vasconcelos 2007) were cross-over trials, we used the generic inverse variance method to calculate effect estimates.

Primary outcome measure: activity limitation

The effect of modafinil on activity limitations was only investigated in the Vasconcelos trial (Vasconcelos 2007). Results of this study showed that there was no significant difference in activity limitations as measured with the SF-36 PF between modafinil treatment and placebo (MD 1.28; 95% CI -3.56 to 6.12) (Analysis 1.1).

Secondary outcome measures: muscle strength, muscle endurance, fatigue and pain

Pooling of data on fatigue was not possible, because the results of the Chan study (Chan 2006) were expressed as percentages of baseline values. The Vasconcelos study (Vasconcelos 2007) showed that there were no significant differences in fatigue between modafinil treatment and placebo treatment on any of the scales (Fatigue Severity Scale (FSS): MD 0.39; 95% CI -0.24 to 1.02) (Analysis 1.3); (Visual Analog Scale for Fatigue (VASF): MD -0.01; 95% CI -0.93 to 0.91) (Analysis 1.4); (Fatigue Impact Scale (FIS): MD -3.32; 95% CI -15.22 to 8.58) (Analysis 1.5). The Chan study (Chan 2006) showed significantly less fatigue in the placebo group as compared to the modafinil group (Piper Fatigue Scale (PFS): MD 12.00; 95% CI 4.16 to 19.84) (Analysis 1.2). Also, no significant difference in pain was found between modafinil treatment and placebo treatment (MD 1.21; 95% CI -7.77 to 10.19) (Analysis 1.6) (Vasconcelos 2007). Muscle strength and endurance were not measured.

IVIG

The Farbu study (Farbu 2007) did not report change from baseline scores and therefore final scores are used in the analyses. For both studies (Farbu 2007; Gonzalez 2006), outcomes assessed three months after the (last) infusion were used in the analyses.

Primary outcome measure: activity limitation

The effect of IVIG on activity limitations was only investigated in the Gonzalez trial (Gonzalez 2006). Results of this study showed that there was no significant difference in improvement of activity limitations between the IVIG group and the placebo group as measured with the SF-36 Physical Component Summary (MD 2.30; 95% CI -0.35 to 4.95) (Analysis 2.1).

Secondary outcome measures: muscle strength, muscle endurance, fatigue and pain

Both studies measured isometric muscle strength. Gonzalez 2006 tested muscle strength of (1) a selected 'study-muscle' in the upper leg, lower leg or hand (i.e. a clinically chosen polio-affected muscle with approximately 25% to 75% of what would be the expected strength for the age and sex of the patient) and (2) the remaining muscles that were not selected as the study muscle. In this second outcome measure, different muscle groups of individual patients were recorded as multiple observations for the same outcome. Therefore we could only include the 'study muscle' in our analyses. Farbu 2007 tested muscle strength of knee extensors and elbow flexors bilaterally. As the outcome measures on muscle strength of both studies differ with respect to being symptomatic or not, we decided by consensus that it was not justified to pool these measures. Gonzalez 2006 demonstrated that the IVIG group showed significant improvement in muscle strength compared to placebo (MD 8.60; 95% CI 2.81 to 14.39) (Analysis 2.2.). In Farbu 2007 there were no significant differences in muscle strength between the groups on all four measures (elbow flexion right: MD 0.00; 95% CI -9.57 to 9.57) (Analysis 2.3); (elbow flexion left: MD 0.30; 95% CI -13.31 to 13.91) (Analysis 2.4); (knee extension right: MD 12.90; 95% CI -29.83 to 55.63) (Analysis 2.5); (knee extension left: MD 3.60; 95% CI -44.79 to 51.99) (Analysis 2.6). Fatigue was measured with the Multidimensional Fatigue Inventory (MFI) in Gonzalez 2006 and with the FSS in Farbu 2007. Meta-analysis was not possible as Gonzalez 2006 used change from baseline scores and Farbu 2007 used final scores, which can not be combined as standardised mean differences (Deeks 2008). Both studies showed that there were no significant differences in change of fatigue (MFI: MD 0.00; 95% CI -1.05 to 1.05) (Analysis 2.7) and fatigue post-treatment (FSS: MD -0.60; 95% CI -1.87 to 0.67) (Analysis 2.8) between the groups. Meta-analysis showed no significant difference in pain measured with the VAS scale between patients treated with IVIG and placebo (MD -15.39; 95% CI -45.16 to 14.38) (Analysis 2.9). Farbu 2007 did not demonstrate a significant difference in pain measured with the Pain Drawing Inventory (PDI) three months post-treatment (MD -6.70; 95% CI -23.63 to 10.23) (Analysis 2.10). Muscle endurance was not

measured.

Pyridostigmine

Primary outcome measure: activity limitation

The effect of pyridostigmine on activity limitations was only investigated in Trojan 1999. Results show that there was no significant difference in improvement of activity limitations between the pyridostigmine group and the placebo group as measured with the SF-36 PF (MD 2.10; 95% CI -3.64 to 7.84) (Analysis 3.1).

Secondary outcome measures: muscle strength, muscle endurance, fatigue and pain

Both studies (Horemans 2003; Trojan 1999) measured isometric muscle strength. Horemans 2003 tested the symptomatic quadriceps muscle (i.e. quadriceps with new neuromuscular symptoms, neuromuscular transmission defects and a minimum strength of 30 Nm). Trojan 1999 tested twelve muscle groups and divided them into three categories of weakness. For each patient, a mean value of percent change in muscle strength for each category was calculated. Because of these substantial differences in assessment of muscle strength, we decided by consensus not to pool these data. In both studies there were no significant differences in improvement in muscle strength between the pyridostigmine and placebo group on any of the measures (very weak muscles: MD 33.90; 95% CI -5.49 to 73.29)(Analysis 3.2); (weak muscles: MD -1.80; 95% CI -11.75 to 8.15) (Analysis 3.3); (relative strong muscles: MD -0.30; 95% CI -4.22 to 3.62) (Analysis 3.4); (symptomatic quadriceps muscle: MD 6.70; 95% CI -2.19 to 15.59) (Analysis 3.5)). Muscle endurance was only evaluated in Horemans 2003. Results show that there were no significant differences in muscle endurance (i.e. fatigability during a 30 s sustained contraction of the quadriceps muscle) between the two groups (MD -0.70; 95% CI -2.52 to 1.12) (Analysis 3.6). Meta-analyses of the FSS-results of both trials showed no significant difference in improvement in fatigue between the pyridostigmine group and the placebo group (MD -0.06; 95% CI -0.34 to 0.21) (Analysis 3.7). Also, no significant differences in fatigue improvement were found when measured with the Hare Fatigue Symptom Scale (HFSS) (MD 0.07; 95% CI -0.17 to 0.31) (Analysis 3.8)(Trojan 1999) and the NHP-Energy (MD 1.10; 95% CI -16.24 to 18.44) (Analysis 3.9)(Horemans 2003). Trojan 1999 showed that there were no significant differences between the groups in pain improvement as measured with the SF-36 Bodily Pain (SF-36 BP) (MD -2.10; 95% CI -9.16 to 4.96) (Analysis 3.10).

Lamotrigine

On 2005 did not report change from baseline scores and therefore final scores were used in the analyses. It should be noted that there was a baseline imbalance in all three fatigue measures with more fatigue in the lamotrigine group.

Primary outcome measure: activity limitation

The group that received lamotrigine reported fewer problems in activity limitations, as measured by the NHP-PM after four weeks of treatment, compared to the control group (MD -23.70; 95% CI -35.35 to -12.05) (Analysis 4.1).

Secondary outcome measures: muscle strength, muscle endurance, fatigue and pain

Post-treatment fatigue (assessed with the FSS and NHP-Energy) was lower in the group that received lamotrigine compared to the control group (FSS: MD -1.40; 95% CI -2.26 to -0.54) (Analysis 4.2); (NHP-Energy: MD -33.30; 95% CI -53.13 to -13.47) (Analysis 4.4) despite the higher fatigue levels at baseline in the lamotrigine group. However, results of the VAS scale did not show a significant difference between the two groups (MD -1.00; 95% CI -3.30 to 1.30) (Analysis 4.3). Results showed less pain post-treatment in the lamotrigine group compared to the control group (VAS: MD -2.80; 95% CI -4.36 to -1.24) (Analysis 4.5); (NHP-Pain: MD -30.50; 95% CI -42.72 to -18.28) (Analysis 4.6). Muscle strength and endurance were not measured.

Amantadine

Primary outcome measure: activity limitation

Activity limitations were not measured in the included trial (Stein 1995).

Secondary outcome measures: muscle strength, muscle endurance, fatigue and pain

The study of Stein (Stein 1995) showed that there were no significant differences between the amantadine group and the placebo group in fatigue improvement post-treatment (RR 2.55; 95% CI 0.81 to 7.95) (Analysis 5.1). Muscle strength, muscle endurance and pain were not measured.

Prednisone

Primary outcome measure: activity limitation

Activity limitations were not measured in the included trial (Dinsmore 1995).

Secondary outcome measures: muscle strength, muscle endurance, fatigue and pain

In the study of Dinsmore (Dinsmore 1995), there was no significant difference between the prednisone group and the placebo group in fatigue improvement at three months of treatment (RR 1.13; 95% CI 0.75 to 1.70) (Analysis 6.1). Data on muscle strength were not adequately reported and could not be obtained from the authors because all raw data were discarded. Muscle endurance and pain were not measured.

Muscle strengthening

Primary outcome measure: activity limitation

Activity limitations were not measured in the included trial (Chan 2003).

Secondary outcome measures: muscle strength, muscle endurance, fatigue, pain and adverse events

Chan (Chan 2003) demonstrated that 12 weeks of progressive resistance training of the thenar muscles resulted in significantly more improvement in isometric muscle strength as compared to a group that received no training (MD 39.00; 95% CI 6.12 to 71.88) (Analysis 7.1). Deleterious effects of this training on motor unit survival were investigated through motor unit number estimates (MUNE). Results show that the MUNE did not change at the end of the training. Muscle endurance, fatigue and pain were not measured.

Rehabilitation in warm and cold climates

The study of Strumse (Strumse 2003) did not report change from baseline scores and therefore final scores are used in the analyses. It must be noted that there was a baseline imbalance on both measures of activity limitations between the usual care group and the group that received rehabilitation in a cold climate, with less activity limitations for the usual care group. Because outcome measurements for the usual care group were not done directly post-treatment, three months post-treatment results were used in the analyses.

Primary outcome measure: activity limitation

The group that received usual care reported less problems in activity limitations three months post-treatment compared to the group that received rehabilitation in a cold climate (Sunnaas ADL: MD -2.70; 95% CI -4.53 to -0.87) (Analysis 8.1); (Rivermead Mobility Index (RMI): MD -1.50; 95% CI -2.93 to -0.07) (Analysis 8.3). These differences were maintained six months post-treatment (Sunnaas ADL: MD -2.90; 95% CI -4.73 to -1.07) (Analysis 8.2); (RMI: MD -1.80; 95% CI -3.19 to -0.41) (Analysis 8.4). The baseline imbalance in favour of the usual care group probably biased these results. Rehabilitation in a warm climate did not demonstrate any significant differences in activity limitations on both scales as compared to the usual care group at three months (Sunnaas ADL: MD -1.70; 95% CI -3.47 to 0.07) (Analysis 9.1); (RMI: MD -0.90; 95% CI -2.28 to 0.48) (Analysis 9.2).

Secondary outcome measures: muscle strength, muscle endurance, fatigue, pain and adverse events

Neither rehabilitation in a cold climate nor rehabilitation in a warm climate demonstrated any significant differences in hand-grip strength three months post-treatment as compared to the usual care group (hand grip strength right: MD -5.00; 95% CI -21.82 to 11.82)(Analysis 8.5); (hand grip strength left: MD 5.00; 95% CI -11.21 to 21.21)(Analysis 8.6); (hand grip strength right: MD 2.00; 95% CI -15.15 to 19.15) (Analysis 9.3); (hand grip strength left: MD 6.00; 95% CI -9.10 to 21.10) (Analysis 9.4). Also, both rehabilitation groups did not demonstrate any significant differences in fatigue and pain three months post-treatment as compared to the usual care group (FSS: MD 0.10; 95% CI -0.47 to 0.67) (Analysis 8.7); (VAS: MD 11.00; 95% CI -0.98 to 22.98) (Analysis 8.8); (FSS: MD -0.40; 95% CI -1.02 to 0.22) (Analysis 9.5); (VAS: MD -5.00; 95% CI -16.88 to 6.88)(Analysis 9.6). Muscle endurance and adverse events were not measured.

Static magnetic fields

Primary outcome measure: activity limitation

Activity limitations were not measured in the included trial (Vallbona 1997).

Secondary outcome measures: muscle strength, muscle endurance, fatigue, pain and adverse events

The Vallbona study (Vallbona 1997) demonstrated that the application of static magnetic fields over an identified trigger point results in significantly more pain reduction immediately after application as compared to placebo (MD 4.10; 95% CI 2.75 to 5.45)(Analysis 10.1). There were no adverse events reported directly after treatment. Muscle strength, muscle endurance and fatigue were not measured.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

IVIG versus placebo for postpolio syndrome

Patient or population: patients with postpolio syndrome
Settings:
Intervention: IVIG versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	IVIG versus placebo				
Change in activity limitations Measured with the SF-36 PCS[1]. Scale from: 0 to 100. Follow-up: 3 months	The mean change in activity limitations in the control groups was **-0.8** [2]	The mean Change in activity limitations in the intervention groups was **2.3 higher** (0.35 lower to 4.95 higher)		135 (1 study)	⊕⊕⊕◯ **moderate**[3]	
Adverse events	See comment	See comment	Not estimable	162 (2 studies)	See comment	See additional table 1

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] SF-36 PCS: Short Form-36 Health Survey Physical Component Summary. Higher scores represent fewer activity limitations.
[2] The control group received placebo.

[3] Likely that blinding was broken because of the side effects of the treatment. However, because the result is negative, it is uncertain if unblinding did actually influence this result.

Pyridostigmine versus placebo for postpolio syndrome

Patient or population: patients with postpolio syndrome
Settings:
Intervention: Pyridostigmine versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Pyridostigmine versus placebo				
Change in activity limitations Measured with the SF-36 PF[1]. Scale from: 0 to 100. Follow-up: 6 months	The mean change in activity limitations in the control groups was **1.1** [2]	The mean Change in activity limitations in the intervention groups was **2.1 higher** (3.64 lower to 7.84 higher)		124 (1 study)	⊕⊕⊕◯ **moderate**[3]	
Adverse events	See comment	See comment	Not estimable	193 (2 studies)	See comment	See additional table 1

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] SF-36 PCS: Short Form-36 Health Survey Physical Functioning scale. Higher scores represent fewer activity limitations.
[2] The control group received placebo.

[3] Analysis on effectiveness of blinding provided evidence for unblinding. However, because the result is negative, it is uncertain if unblinding did actually influence this result.

Lamotrigine versus control for postpolio syndrome

Patient or population: patients with postpolio syndrome
Settings:
Intervention: Lamotrigine versus control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Lamotrigine versus control				
Activity limitations post-treatment Measured with the NHP-PM[1]. Scale from: 0 to 100. Follow-up: 4 weeks	The mean activity limitations post-treatment in the control groups was **38.4** [2]	The mean Activity limitations post-treatment in the intervention groups was **23.7 lower** (35.35 to 12.05 lower)		30 (1 study)	⊕○○○ **very low**[3,4]	
Adverse events	See comment	See comment	Not estimable	30 (1 study)	See comment	See additional table 1

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] NHP-PM: Nottingham Health Profile-Physical Mobility. Higher scores represent more activity limitations.
[2] The control group received usual care (advice on pacing, energy conservation, use of orthotic devices and weight loss and recommendation to start a home exercise program).

[3] Open-label study and therefore no blinding. Randomisation procedure is unclear. Insufficient reporting on incomplete outcome data.
[4] Small sample size (n = 30).

Amantadine versus placebo for postpolio syndrome

Patient or population: patients with postpolio syndrome
Settings:
Intervention: Amantadine versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Amantadine versus placebo				
Activity limitations - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Adverse events	See comment	See comment	Not estimable	25 (1 study)	See comment	See additional table 1

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Prednisone versus placebo for postpolio syndrome

Patient or population: patients with postpolio syndrome
Settings:
Intervention: Prednisone versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Prednisone versus placebo				
Activity limitations - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Adverse events	See comment	See comment	Not estimable	17 (1 study)	See comment	See additional table 1

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Muscle strengthening versus control for postpolio syndrome

Patient or population: patients with postpolio syndrome
Settings:
Intervention: Muscle strengthening versus control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Muscle strengthening versus control				
Activity limitations - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Adverse events	See comment	See comment	Not estimable	10 (1 study)	See comment	Deleterious effects on motor unit survival were investigated through motor unit number estimates (MUNE). Results show that MUNE did not change after training.

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Rehabilitation in cold climate versus usual care for postpolio syndrome

Patient or population: patients with postpolio syndrome
Settings:
Intervention: Rehabilitation in cold climate versus usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Rehabilitation in cold climate versus usual care				
Activity limitations 3 months post-treatment Measured with the Sunnaas ADL-index[1]. Scale from: 0 to 36.	The mean activity limitations 3 months post-treatment in the control groups was **32.6** [2]	The mean Activity limitations 3 months post-treatment in the intervention groups was **2.7 lower** (4.53 to 0.87 lower)		53 (1 study)	⊕⊕◯◯ **low**[3]	
Activity limitations 6 months post-treatment Measured with the Sunnaas ADL-index[1]. Scale from: 0 to 36.	The mean activity limitations 6 months post-treatment in the control groups was **32.4** [2]	The mean Activity limitations 6 months post-treatment in the intervention groups was **2.9 lower** (4.73 to 1.07 lower)		53 (1 study)	⊕⊕◯◯ **low**[3]	
Activity limitations 3 months post-treatment Measured with the Rivermead Mobility Index [4]. Scale from: 0 to 15.	The mean activity limitations 3 months post-treatment in the control groups was **13.2** [2]	The mean Activity limitations 3 months post-treatment in the intervention groups was **1.5 lower** (2.93 to 0.07 lower)		53 (1 study)	⊕⊕◯◯ **low**[3]	

Activity limitations 6 months post-treatment Measured with the Rivermead Mobility Index[4]. Scale from: 0 to 15.	The mean activity limitations 6 months post-treatment in the control groups was **13.5** [2]	The mean Activity limitations 6 months post-treatment in the intervention groups was **1.8 lower** (3.19 to 0.41 lower)		53 (1 study)	⊕⊕◯◯ **low**[3]	
Adverse events - not measured	See comment	See comment	Not estimable	-	See comment	Not measured

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Sunnaas ADL: Sunaas Index of Activities of Daily Living. Higher scores represent fewer activity limitations.
[2] The control group received usual care in a cold climate (rainy or snowy, temperature around 0 degree C).
[3] The combination of the baseline imbalance in activity limitations scores and the fact that only post-treatment scores (and not change scores) are available reduces the quality of evidence. Randomisation procedure is unclear, blinding not possible.
[4] Rivermead mobility index: higher scores represent fewer activity limitations.

Rehabilitation in warm climate versus usual care for postpolio syndrome

Patient or population: patients with postpolio syndrome
Settings:
Intervention: Rehabilitation in warm climate versus usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Rehabilitation in warm climate versus usual care				
Activity limitations 3 months post-treatment Measured with the Sunnaas ADL-index[1]. Scale from: 0 to 36.	The mean activity limitations 3 months post-treatment in the control groups was **32.6** [2]	The mean Activity limitations 3 months post-treatment in the intervention groups was **1.7 lower** (3.47 lower to 0.07 higher)		57 (1 study)	⊕⊕◯◯ **low**[3]	
Activity limitations 3 months post-treatment Measured with the Rivermead Mobility Index[4]. Scale from: 0 to 15.	The mean activity limitations 3 months post-treatment in the control groups was **13.2** [2]	The mean Activity limitations 3 months post-treatment in the intervention groups was **0.9 lower** (2.28 lower to 0.48 higher)		57 (1 study)	⊕⊕◯◯ **low**[3]	
Adverse events - not measured	See comment	See comment	Not estimable	-	See comment	Not measured

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Sunnaas ADL: Sunaas Index of Activities of Daily Living. Higher scores represent fewer activity limitations.
[2] The control group received usual care in a cold climate (rainy or snowy, temperature around 0 degree C).
[3] Randomisation procedure is unclear. Blinding not possible.
[4] Rivermead mobility index: higher scores represent fewer activity limitations.

Static magnetic fields versus placebo for postpolio syndrome

Patient or population: patients with postpolio syndrome
Settings:
Intervention: Static magnetic fields versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Static magnetic fields versus placebo				
Activity limitations - not measured	See comment	See comment	Not estimable	-	See comment	Not measured
Adverse events	See comment	See comment	Not estimable	50 (1 study)	See comment	No adverse events reported directly after treatment

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

DISCUSSION

Summary of main results

Modafinil

Results of the study of Chan 2006 and Vasconcelos 2007 showed that treatment with modafinil at a daily dose of 400 mg does not reduce activity limitations, fatigue and pain as compared to placebo and causes adverse events in a substantial proportion of the *verum* group. From the limited but high quality evidence, it can be concluded that there is no beneficial effect of modafinil. See Summary of findings for the main comparison.

IVIG

Treatment with IVIG (two infusions of 90 g or one infusion of 2 g/kg body weight) has no beneficial effect on activity limitations and fatigue (Gonzalez 2006; Farbu 2007). The effects on muscle strength are inconsistent; the Gonzalez study (Gonzalez 2006) found a significant improvement in strength as compared to placebo, in contrast to Farbu 2007. This inconsistency might be explained by the fact that the results of Gonzalez 2006 are based on effects in symptomatic muscles whereas the results of Farbu 2007 are based on four preselected muscle groups irrespective of being symptomatic or not. Gonzalez 2006 reported that the beneficial effect of IVIG was not demonstrable in muscles that were not selected as the (symptomatic) study muscle. As mentioned in our results section, we could not, unfortunately, include these data in our analyses. Another remarkable point reported by Gonzalez 2006 was the finding that the degree of decline in muscle strength in the placebo group was considerably higher than in previous reports on the natural course of untreated PPS patients. This might possibly be explained by differences in the study populations in these studies or more specific differences in the study muscles. The analyses of this review showed that IVIG did not have any effect on pain, which is in contrast with the conclusions of Farbu 2007. The beneficial effect on pain in Farbu 2007 was not upheld after pooling data with the non-significant results of the much larger Gonzalez study (Gonzalez 2006). The difference between the two studies might be explained by the finding that the patients from the Farbu trial experienced more pain at baseline as compared to the patients of the Gonzalez trial. This explanation is supported by the positive results of IVIG on pain in a subgroup of patients from the trial of Gonzalez that report significant pain (i.e. 20 mm or more out of 100 mm on the VAS scale). However, it must be realised that unblinding of patients due to side effects of IVIG may have introduced bias, resulting in an overestimation of the beneficial effect on pain. In conclusion, there is moderate quality evidence that IVIG has no beneficial effect on activity limitations and there is inconsistency in the evidence for effectiveness of IVIG on muscle strength and pain. IVIG causes adverse events in a substantial proportion of the treated patients. More studies are needed to further clarify these findings. See Summary of findings 2.

Pyridostigmine

Pyridostigmine at a daily dose of 180 mg or 240 mg has no beneficial effects on activity limitations, muscle function, fatigue and pain and causes adverse events in a substantial proportion of the treated patients (Horemans 2003; Trojan 1999). It can be concluded that there is moderate quality evidence of no beneficial effect for the prescription of a fixed dose of pyridostigmine of 180 or 240 mg. See Summary of findings 3. As it is known that for the treatment of muscle weakness in myasthenia gravis, daily dosages up to 540 to 720 mg may be administered and plasma concentrations of this drug can vary greatly between individuals, it would be valuable to investigate the effects of individually adjusted doses of pyridostigmine on symptoms of PPS.

Lamotrigine

There is very low quality evidence that lamotrigine at a daily dose of 50 to 100 mg has a positive effect on activity limitations and pain after four weeks of treatment, without generating adverse effects (On 2005). See Summary of findings 4. The beneficial effects on fatigue are inconsistent as two fatigue scales showed less fatigue in the medication group compared to the control group post-treatment, but on another fatigue scale no significant difference was found. A major limitation of this study is the relatively short treatment period of only four weeks. Furthermore the potential biases associated with the open-label design of the study using patient-reported outcomes, probably compromised the validity. Therefore placebo-controlled studies with larger sample sizes, a longer follow-up period and adequate blinding are needed to establish the efficacy of lamotrigine.

Amantadine

Six weeks of treatment with 200 mg amantadine per day does not reduce fatigue as compared to placebo and causes side effects in a substantial proportion of the medication group (Stein 1995). The authors state that there was no association found between serum amantadine level and clinical response. Results of this study are based on a small sample size. It can be concluded that there is very low quality evidence of no beneficial effect of amantadine for the treatment of fatigue in PPS. See Summary of findings 5.

Prednisone

High dose (80 mg/day for four weeks followed by a 20-week tapering scheme) prednisone has no beneficial effect on fatigue (Dinsmore 1995). It is of note that both the patients treated in the prednisone group as well as in the placebo group frequently developed (glucocorticoid-like) adverse events and in three cases even led to cessation of treatment. Results of this study are based

on a small sample size. It can be concluded that there is very low quality evidence of no beneficial effect of high-dose prednisone for the treatment of fatigue in PPS. See Summary of findings 6.

Muscle strengthening

Progressive resistance training of thumb muscles affected by polio has a beneficial effect on muscle strength (Chan 2003). To investigate whether the effects of strength training in PPS is comparable to that seen in healthy elderly, in Chan 2003 seven healthy elderly were also randomised and trained in a similar manner. Trial authors conclude that even though PPS subjects are weaker than the healthy elderly, they are capable of showing an improvement in their muscle strength in response to training that exceeds that of the healthy subjects. Also, the study proves that training did not adversely affect motor unit survival. In this study only ten patients were included, and blinding was not possible. Therefore, it can be concluded that there is very low quality evidence that progressive resistance training of thumb muscles has a beneficial effect on muscle strength. See Summary of findings 7. It would be valuable to investigate whether strength training of larger muscle groups like the lower limb muscles, which are mostly affected in PPS, would lead to the same results. Also, effects of resistance training on activity limitations and long term effects need to be evaluated in further studies.

Rehabilitation in warm and cold climates

Rehabilitation treatment in a warm climate (temperature ± 25°C, dry and sunny) does not reduce activity limitation problems, or improve muscle strength, fatigue and pain as compared to usual care (Strumse 2003). The beneficial effect of usual care on activity limitations as compared to rehabilitation treatment in a cold climate (i.e. temperature ± 0°C, rainy or snowy) is probably the result of a baseline imbalance. This assumption is supported by the finding that usual care did not have a beneficial effect on muscle strength, fatigue and pain compared to treatment in a cold climate. A more detailed description of the different components of the program and an outcome assessment for the usual care group directly posttreatment, would have given more insight in the short term individual effects of both rehabilitation groups and might have led to a better understanding of the results found in this study. In conclusion, there is low quality evidence of no beneficial effect of rehabilitation treatment in warm and cold climates three months after treatment. See Summary of findings 8 and Summary of findings 9.

Static magnetic fields

There is moderate quality evidence of beneficial effect of application of static magnetic fields over a pain trigger point in reducing pain directly after treatment without generating adverse events (Vallbona 1997). See Summary of findings 10. The clinical relevancy of the immediate effect on pain is unclear since sustained effects were not investigated. Therefore, effects on activity limitations and long term effects need to be evaluated in further studies.

Overall completeness and applicability of evidence

In this review, we included studies on ten different interventions, both pharmacological as well as non-pharmacological. However, a considerable number of intervention studies were excluded, mainly because the design of these studies did not meet our prespecified criteria. Excluded pharmacological studies included those on the effect of bromocriptine, IGF-I, human growth hormone, coenzyme Q10 and selegiline. The preliminary evidence from these studies indicates that those interventions are not effective (Miller 1997; Skough 2008) or might cause serious adverse events (Bamford 1993; Bruno 1996). This may explain why these pharmacological interventions were never investigated in larger properly controlled studies. Excluded non-pharmacological studies included those on the effectiveness of aerobic exercise, hydrotraining, respiratory muscle training, respiratory support, orthoses, lifestyle changes and weight control. All these interventions are recommended to a certain degree by the EFNS task force (Farbu 2006) and these recommendations are based on consensus within the task force group or on studies that could not be included in this review.

Quality of the evidence

Both the amount of evidence as well as the quality of evidence in this review is limited.

For each of the ten different interventions evaluated in this review, evidence is based on only one or two included studies. The quality of evidence in this review was rather low for several reasons. Blinding of participants and administrators of the intervention was a prevalent risk of bias. Admittedly, blinding is cumbersome in trials on physical treatment and in trials with medication with substantial adverse events. In addition, many of these trials used patient-reported outcomes, which make blinded outcome assessment not feasible.

We also noted that there are a large number of negative (i.e. non-significant) results. The most reasonable explanation for this finding is that the investigated interventions actually have no effects. This might partially be explained by the fact that targeting interventions is very difficult when the exact pathogenesis of a disorder is still unclear as is the case with PPS.

However, other possible explanations have been brought up, explaining the large amount of negative results in intervention studies in PPS (Dalakas 1999; Nollet 2000; Nollet 2010). Firstly, there is a risk of misdiagnosis since PPS is a diagnosis per exclusionem. Secondly, patients with PPS constitute a highly heterogeneous group, which may hinder balanced randomisation in a trial.

Thirdly, the duration of treatment might be a problem. The slow progression in PPS warrants long-term follow-up for interventions aimed at preventing deterioration in signs and symptoms. Finally, relevant outcome measures are lacking. For example, most of the questionnaires used in PPS research are generic, non-disease specific measures, which might not be responsive enough to detect relevant changes.

Potential biases in the review process

We probably identified all relevant studies in this review, because there are not so many experts in this field and we supplemented our search strategy with checking references, searching databases of ongoing trials and contacting experts.

The fact that there was almost complete consensus between the two review authors responsible for study selection, suggests that the risk of selection bias in this part of the review process is probably low.

In a considerable number of studies it was unclear whether participants met our inclusion criteria for the diagnosis of PPS. Also, many studies did not report outcomes in such a way that it could be used in our analyses. All but one trial author responded to our requests for further information on these topics and the trial authors were able to provide most of the requested information.

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate quality evidence that IVIG has no beneficial effect on activity limitations and there is inconsistency in the evidence for effectiveness of IVIG on muscle strength and pain. Results of one trial provide very low quality evidence that lamotrigine might be effective in reducing pain and fatigue, resulting in fewer activity limitations. Data from two single trials suggest that muscle strengthening of thumb muscles (very low quality evidence) and static magnetic fields (moderate quality evidence) are beneficial for improving muscle strength and pain, respectively, with unknown effects on activity limitations. Finally, there is evidence varying from very low quality to high quality that modafinil, pyridostigmine, amantadine, prednisone and rehabilitation in a warm or cold climate are not beneficial in PPS. However, due to insufficient good quality data and lack of randomised studies it is impossible to draw definite conclusions on the effectiveness of interventions in people with PPS.

Implications for research

More evidence is needed to investigate the effects of IVIG and lamotrigine for patients with PPS. Muscle strengthening of varying intensity and muscle groups and (long-term) effects on activity limitations should be evaluated in the future. Although this review could not demonstrate a positive effect of rehabilitation in a warm or cold climate in PPS, further studies should evaluate the effects of comprehensive rehabilitation with varying program components. It is also recommended that in further studies on the effect of climate, differences between treatment and 'living' in a particular climate are taken into account. It might be valuable to investigate the effect of individually adjusted doses of pyridostigmine and the long term effects of static magnetic fields on pain and activity limitations. Finally, other possible treatments not evaluated in this review, such as orthoses, lifestyle changes and aerobic exercise should be tested in randomised controlled trials, and monitoring and reporting of adverse effects of both pharmacological and non-pharmacological interventions should be systematically addressed.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chan 2003

Methods	Randomised, controlled trial
Participants	N = 10 (strength training 5, no training 5) Mean age: 65 years (strength training), 65 years (no training) Gender distribution, male (%): 20% (strength training), 0% (no training) Inclusion: unequivocal history of prior poliomyelitis in an otherwise healthy subject, one or both upper limbs affected by polio, further strength decline after stable period, moderate motor neuronal loss in the median-innervated thenar muscles (motor unit number estimates (MUNE) between 10 and 90)
Interventions	Treatment intervention: supervised progressive resistance training consisting of three sets of eight isometric contractions of the thumb muscles, three times weekly for 12 weeks. Training load 50 to 70% MVC. Control intervention: no training
Outcomes	Measurements at baseline, 4, 8 and 12 weeks. Outcomes: muscle function of thumb muscles: isometric strength, voluntary activation, MUNE, tetanic tension
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"Randomisation was done using the random number generation function in a commercially available software program."
Allocation concealment?	Unclear risk	No information
Blinding? All outcomes - patients?	High risk	Not possible
Blinding? All outcomes - administrators of the intervention?	High risk	Not possible
Blinding? All outcomes - outcome assessors?	Unclear risk	No information
Incomplete outcome data addressed? Missing outcome data?	Unclear risk	Insufficient reporting

Chan 2003 (*Continued*)

Incomplete outcome data addressed? ITT-analyses performed?	Unclear risk	Insufficient reporting
Free of selective reporting?	Unclear risk	Study protocol is not available
Free of other bias?	Low risk	

Chan 2006

Methods	Randomised, double-blinded, placebo-controlled, cross-over trial
Participants	N = 14 (phase 1: modafinil 7, placebo 7; phase 2: modafinil 7, placebo 7) Mean age: 57.7 years Gender distribution, male (%): 36% Inclusion: unequivocal history of polio, new neuromuscular symptoms after stable period, moderate to severe fatigue Exclusion: presence of any medical condition or medication that could influence level of fatigue
Interventions	Treatment intervention: a 5-week course of modafinil of maximal 200 mg 2 times per day. From day 14, subjects were given the option of adjusting their daily dosage between 200 mg and 400 mg based on how they felt Control intervention: placebo Wash-out interval: 1 week
Outcomes	Measurements at baseline, and at weekly intervals throughout the study Primary: fatigue (Piper Fatigue Scale) Secondary: daytime sleepiness (Epworth Sleepiness Scale), short term memory (forward and backward aural digit span test), reaction time
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Insufficient reporting
Allocation concealment?	Low risk	"The randomisation code was generated by Draxis Pharmaceuticals, which was not otherwise directly involved in the study. Neither the subjects nor the investigators had access to the sealed codes."
Blinding? All outcomes - patients?	Low risk	"Subjects were randomised in a double blind manner" Comment: although there were more side effects experienced during modafinil treat-

Chan 2006 (*Continued*)

		ment, analysis on effectiveness of blinding provided evidence for successful blinding (57% correct guessing)
Blinding? All outcomes - administrators of the intervention?	Low risk	"Subjects were randomised in a double blind manner" and "neither the subjects nor the investigators had access to the sealed codes"
Blinding? All outcomes - outcome assessors?	Low risk	"Subjects were randomised in a double blind manner" and "neither the subjects nor the investigators had access to the sealed codes"
Incomplete outcome data addressed? Missing outcome data?	Unclear risk	Insufficient reporting; although all 14 subjects completed the trial, it is unclear whether they all completed the outcome measurements.
Incomplete outcome data addressed? ITT-analyses performed?	Unclear risk	Insufficient reporting
Free of selective reporting?	Unclear risk	Study protocol is not available
Free of other bias?	Low risk	Because PPS is considered a reasonably stable chronic condition and modafinil is a medicament with a temporary effect, we considered the use of a cross-over design appropriate

Dinsmore 1995

Methods	Randomised, double-blinded, placebo-controlled trial
Participants	N = 17 (high-dose prednisone 9, placebo 8) Mean age: 50.2 years (high-dose prednisone), 47.8 years (placebo) Gender distribution, male: 56% (high-dose prednisone), 38% (placebo) Inclusion: history of acute paralytic poliomyelitis, followed by 10 to 20 years of stable neuromuscular function, followed by new muscle weakness unrelated to other cause Exclusion: contraindications to receive steroids, medical diseases causing fatigue, major depression, older than 60 years
Interventions	Treatment intervention: 4 weeks of prednisone 80 mg once daily continued by a 20 weeks dose reduction schedule. From week 25 discontinuation Control intervention: placebo
Outcomes	Measurements at baseline, 3 months (primary) and 6 months Primary: muscle strength (Tufts Quantitative Neuromuscular Examination)

Dinsmore 1995 (*Continued*)

	Secondary: muscle strength (MMT), fatigue (4 point scale)	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No information
Allocation concealment?	Low risk	"NIH Pharmacy performed the randomisation and maintained blinding to treatment assignment"
Blinding? All outcomes - patients?	Low risk	"The patients were blinded to treatment assignment" Comment: side effects were experienced in both groups, therefore unlikely that this have led to unblinding
Blinding? All outcomes - administrators of the intervention?	Low risk	"Treating physicians were blinded to treatment assignment" Comment: side effects were experienced in both groups, therefore unlikely that this have led to unblinding
Blinding? All outcomes - outcome assessors?	Low risk	"Staff performing muscle strength evaluations was blinded to treatment assignment"
Incomplete outcome data addressed? Missing outcome data?	High risk	Missing outcomes: high-dose prednisone 2/9, placebo 1/8 Comment: reasons for missing outcome data likely related to true outcome
Incomplete outcome data addressed? ITT-analyses performed?	Unclear risk	Insufficient reporting
Free of selective reporting?	Unclear risk	Study protocol is not available
Free of other bias?	Low risk	

Farbu 2007

Methods	Randomised, double-blinded, placebo-controlled trial
Participants	N = 20 (intravenous immunoglobulin (IVIG) 10, placebo 10) Mean age: 59.9 years (IVIG), 58.7 years (placebo) Gender distribution, male (%): 40% (IVIG), 30% (placebo) Inclusion: diagnosis of PPS according to the criteria of Halstead (1991) Exclusion: wheel chair dependence, cardiac disease, diabetes mellitus, renal insufficiency, warfarin treatment, previous thromboembolic episode, increased thrombotic risk, previous IVIG treatment, IgA deficit, other ongoing autoimmune disease
Interventions	Treatment intervention: one infusion of IVIG with a dose of 2 g/kg body weight Control intervention: placebo
Outcomes	Measurements at baseline, 1 month, 3 months (primary) and 6 months Primary: pain (VAS, Pain Drawing Instrument), fatigue (FSS), isometric muscle strength of elbow flexors and knee extensors Secondary: CSF cytokine levels
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"The hospital pharmacy prepared a randomisation scheme with 20 notes marked with either IvIg or placebo. As the patients were enrolled prospectively, one note was drawn for each patient."
Allocation concealment?	Low risk	"The blinding scheme was kept by the pharmacy and was not broken during the trial."
Blinding? All outcomes - patients?	High risk	"Patients were blinded throughout the study." Comment: likely that blinding was broken because of the side effects of the treatment
Blinding? All outcomes - administrators of the intervention?	High risk	"Study personnel was blinded throughout the study." Comment: likely that blinding was broken because of the side effects of the treatment
Blinding? All outcomes - outcome assessors?	High risk	"Study personnel was blinded throughout the study." Comment: self-reported outcomes are used and blinding of patients could have been broken

Farbu 2007 (*Continued*)

Incomplete outcome data addressed? Missing outcome data?	Low risk	No missing outcome data
Incomplete outcome data addressed? ITT-analyses performed?	Low risk	ITT analyses were probably done since all patients received the intervention to which they were randomised
Free of selective reporting?	Low risk	Study protocol available in trial register (NCT00231439): pre-specified outcomes have been reported
Free of other bias?	Low risk	

Gonzalez 2006

Methods	Randomised, double-blinded, placebo-controlled trial
Participants	N = 142 (intravenous immunoglobulin (IVIG) 73, placebo 69) Mean age: 61.5 years (IVIG), 59.0 years (placebo) Gender distribution, male (%): 29% (IVIG), 42% (placebo) Inclusion: diagnosis of PPS according to the criteria of Halstead and Rossi (1987) with increased muscle weakness, muscle fatigue and pain in muscle groups previously affected by the poliomyelitis, age between 18 and 75 years Exclusion: obesity or unstable weight, other disorders explaining PPS symptoms, S-IgA deficiency
Interventions	Treatment intervention: infusion of 90 g in total of IVIG during 3 consecutive days, repeated after 3 months Control intervention: placebo
Outcomes	Measurements at baseline and 3 months after the second infusion Primary: muscle strength in a selected study muscle, quality of life (SF-36 PCS) Secondary: vitality (SF-36 vitality), 6-minute walk test, timed up and go, muscle strength in muscles not chosen as the study muscle, physical activity (PASE), pain (VAS), fatigue (MFI-20), balance, sleep quality
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"A computer generated list with permuted blocks of randomly varying size (2,4,6) allocated consecutive patient numbers to treatment group"

Gonzalez 2006 (*Continued*)

Allocation concealment?	Low risk	"Randomisation was done by an independent contract research organisation"
Blinding? All outcomes - patients?	High risk	"Patients were unaware of treatment allocation throughout the study." Comment: likely that blinding was broken because of the side effects of the treatment
Blinding? All outcomes - administrators of the intervention?	High risk	"Physicians and nurses were unaware of treatment allocation throughout the study." Comment: likely that blinding was broken because of the side effects of the treatment
Blinding? All outcomes - outcome assessors?	High risk	"Physiotherapists were unaware of treatment allocation throughout the study." Comment: self-reported outcomes are used and blinding of patients could have been broken
Incomplete outcome data addressed? Missing outcome data?	High risk	1/143 received no medication: reason unclear Missing outcomes: IVIG - 6/73, placebo - 1/69 Comment: reason for missing outcome data likely related to true outcome
Incomplete outcome data addressed? ITT-analyses performed?	Low risk	ITT-analyses with the last results carried forward did not differ from the per-protocol analysis
Free of selective reporting?	Low risk	Study protocol available in trial register (NCT00160082): pre-specified outcomes have been reported
Free of other bias?	High risk	Baseline imbalance in gender

Horemans 2003

Methods	Randomised, double-blinded, placebo-controlled trial
Participants	N = 67 (pyridostigmine 34, placebo 33) Mean age: 51 years (pyridostigmine), 52 years (placebo) Gender distribution, male (%): 30% (pyridostigmine), 39% (placebo) Inclusion: symptoms of postpoliomyelitis muscle dysfunction in at least one quadriceps according to the criteria of Borg (1996), neuromuscular transmission defects and minimum strength of 30 Nm in the symptomatic quadriceps, fatigue, age between 18 and 70 years

Horemans 2003 (*Continued*)

	Exclusion: significant neurological, orthopaedic, cardiovascular, pulmonary or endocrine disorders
Interventions	Treatment intervention: a 14-week course of pyridostigmine 60 mg 4 times per day Control intervention: placebo
Outcomes	Measurements at baseline, at 5 and 14 weeks (primary) and at 3 weeks after cessation of treatment Primary: fatigue (NHP-energy) Secondary: fatigue (FSS), 2-minute walk test, 75-meters walk test, daily physical activity (activity monitor), muscle function of quadriceps: isometric strength, voluntary activation, fatigability, transmission defects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No information
Allocation concealment?	Unclear risk	No information
Blinding? All outcomes - patients?	Low risk	"Treatment allocations were concealed for the patients" Comment: extra effort was taken to improve blinding (for example placebo atropine) and analysis on effectiveness of blinding provided evidence for successful blinding
Blinding? All outcomes - administrators of the intervention?	Low risk	"Treatment allocations were concealed for the researchers"
Blinding? All outcomes - outcome assessors?	Low risk	"Treatment allocations were concealed for the researchers" and "The data analyst remained blinded until after the primary outcome analyses."
Incomplete outcome data addressed? Missing outcome data?	High risk	At 14 weeks: Missing outcomes: pyridostigmine - 3/34, placebo - 2/33 Comment: reason for missing outcome data likely related to true outcome
Incomplete outcome data addressed? ITT-analyses performed?	Low risk	"Analyses were based on an ITT approach"

Horemans 2003 (*Continued*)

Free of selective reporting?	Unclear risk	Study protocol is not available
Free of other bias?	Low risk	

On 2005

Methods	Randomised, controlled trial
Participants	N = 30 (lamotrigine + usual care - 15, usual care - 15) Mean age: 36.6 years (lamotrigine + usual care), 35.9 years (usual care) Inclusion: diagnosis of PPS according to the criteria of Halstead and Rossi (1985), lower extremity involvement Exclusion: non-ambulatory or wheelchair dependent patients, medical illnesses that could be contributing to any secondary deterioration in muscle performance
Interventions	Treatment intervention: a 4-week course of lamotrigine of 50 to 100 mg per day + usual care (advice on pacing, energy conservation, use of orthotic devices and weight loss and recommendation of starting a home exercise program) Control intervention: usual care (as described under treatment intervention)
Outcomes	Measurements at baseline, 2 and 4 weeks Outcomes: pain (VAS), fatigue (VAS, FSS), muscle cramps (VAS), HRQoL (NHP-6 dimensions)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No information
Allocation concealment?	Unclear risk	No information
Blinding? All outcomes - patients?	High risk	No blinding
Blinding? All outcomes - administrators of the intervention?	High risk	No blinding
Blinding? All outcomes - outcome assessors?	High risk	Comment: self-reported outcomes are used and patients are not blinded
Incomplete outcome data addressed? Missing outcome data?	Unclear risk	Insufficient reporting

On 2005 (*Continued*)

Incomplete outcome data addressed? ITT-analyses performed?	Unclear risk	Insufficient reporting
Free of selective reporting?	Unclear risk	Study protocol is not available
Free of other bias?	High risk	Baseline imbalance in fatigue severity

Stein 1995

Methods	Randomised, double-blinded, placebo-controlled trial
Participants	N = 25 (amantadine 11, placebo 14) Mean age: range total sample 34 to 59 years Gender distribution, male (%): total sample 76% Inclusion: diagnosis of PPS according to the criteria of Dalakas (1995), prominent fatigue (FSS score > 3). Exclusion: medical conditions or medication which may cause fatigue
Interventions	Treatment intervention: a 6-week course of amantadine of 100 mg two times per day Control intervention: placebo
Outcomes	Measurements at baseline, post-treatment Outcomes: fatigue (VAS, FSS), overall effectiveness, neuropsychological tests
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No information
Allocation concealment?	Unclear risk	No information
Blinding? All outcomes - patients?	High risk	"double-blind study" Comment: not explicitly stated who was blinded and likely that blinding was broken because of the side effects of the treatment
Blinding? All outcomes - administrators of the intervention?	High risk	"double-blind study" Comment: not explicitly stated who was blinded and likely that blinding was broken because of the side effects of the treatment
Blinding? All outcomes - outcome assessors?	High risk	"double-blind study" Comment: not explicitly stated who was blinded and self-reported outcomes are used and blinding of patients could have

Stein 1995 (*Continued*)

		been broken
Incomplete outcome data addressed? Missing outcome data?	Unclear risk	Insufficient reporting
Incomplete outcome data addressed? ITT-analyses performed?	Unclear risk	Insufficient reporting
Free of selective reporting?	Unclear risk	Study protocol is not available.
Free of other bias?	Low risk	

Strumse 2003

Methods	Randomised, controlled trial
Participants	N = 88 (warm climate rehabilitation 30, 'cold' climate rehabilitation 29, usual care 29) Mean age: 57.3 years (warm climate rehabilitation), 57.4 years ('cold' climate rehabilitation), 58.6 years (usual care) Gender distribution, male (%): 27% (warm climate rehabilitation), 31% ('cold' climate rehabilitation), 34% (usual care) Inclusion: diagnosis of PPS according to the criteria of Halstead (1987) Exclusion: other medical conditions that could influence the rehabilitation programme
Interventions	Treatment intervention 1 (warm climate rehabilitation): outdoor treatment in a rehabilitation centre in Tenerife (dry, sunny, temperature around 25°C) consisting of a combination of individual and group therapy with daily treatment in a swimming pool (45 min), physiotherapy, individually adapted training program for 4 weeks Treatment intervention 2 (cold climate rehabilitation): indoor treatment as described above in a rehabilitation centre in Norway (rainy or snowy, temperature around 0°C) Control intervention: usual care in a cold climate as described under treatment intervention 2
Outcomes	Measurements at baseline, post treatment (only intervention 1 and 2), at 3 and 6 months following intervention Outcomes: pain (VAS), fatigue (FSS), health related problems (Ursin Holder Inventorium), depression (BDI), life satisfaction (Life Satisfaction Scale), ADL, (Sunnaas ADL-index), mobility (RMI), lung function (spirometry), handgrip strength, endurance (6-MWT), walking (20-min fast walking), movement (TUG)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	No information

Strumse 2003 (*Continued*)

Allocation concealment?	Unclear risk	No information
Blinding? All outcomes - patients?	High risk	Not possible
Blinding? All outcomes - administrators of the intervention?	High risk	Not possible
Blinding? All outcomes - outcome assessors?	High risk	Patient-reported outcomes included and patients are not blinded. Insufficient reporting of blinding status for objective outcome measures.
Incomplete outcome data addressed? Missing outcome data?	Unclear risk	No information
Incomplete outcome data addressed? ITT-analyses performed?	Low risk	Subjects were analysed in the groups to which they were randomised
Free of selective reporting?	Unclear risk	Study protocol is not available
Free of other bias?	High risk	Baseline imbalance in activity limitations outcomes and no direct post-treatment outcome assessment for the usual care group

Trojan 1999

Methods	Randomised, double-blinded, placebo-controlled trial
Participants	N = 126 (pyridostigmine 64, placebo 62) Mean age: 56.8 years (pyridostigmine), 55.7 years (placebo) Gender distribution, male (%): 34% (pyridostigmine), 45% (placebo) Inclusion: ambulatory, history and physical examination consistent with past paralytic polio followed by at least 10 years of functional stability, new symptoms of general fatigue or muscular fatigue and new weakness of at least 1 year's duration Exclusion: medical conditions that could produce similar symptoms to PPS, contraindications to usage of pyridostigmine
Interventions	Treatment intervention: a 6-month course of pyridostigmine 60 mg three times per day Control intervention: placebo
Outcomes	Measurements at baseline, 6 and 10 weeks and 6 months (primary) Primary: physical functioning (SF-36 PF) Secondary: quality of life (SF-36; 7 remaining scales), isometric muscle strength (modified Tufts Quantitative Neuromuscular Examination), fatigue (Hare Fatigue Symptom Scale, FSS), IGF-I serum levels

Trojan 1999 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"The randomisation scheme was computer generated"
Allocation concealment?	Low risk	"The randomisation scheme was kept at the coordinating centre with a copy at the pharmaceutical and packaging company."
Blinding? All outcomes - patients?	High risk	"Study patients were blinded to patient treatment assignment during the course of the study." Comment: likely that blinding was broken because of the side effects of the treatment "Analysis on effectiveness of blinding provided evidence for unblinding" Comment: authors state that unblinding did probably not influence the results since the study was negative. However unblinding remains a risk of bias
Blinding? All outcomes - administrators of the intervention?	High risk	"Physicians were blinded to patient treatment assignment during the course of the study." Comment: likely that blinding was broken because of the side effects of the treatment "Analysis on effectiveness of blinding provided evidence for unblinding" Comment: authors state that unblinding did probably not influence the results since the study was negative. However unblinding remains a risk of bias
Blinding? All outcomes - outcome assessors?	High risk	"Study personnel were blinded to patient treatment assignment during the course of the study." Comment: self-reported outcomes are used and blinding of patients is probably broken
Incomplete outcome data addressed? Missing outcome data?	Low risk	At 6 months: no drop-outs, some missing data for the main outcome measure per group, no imputation. Reason for missing outcome data unlikely related to true outcome

Trojan 1999 (*Continued*)

Incomplete outcome data addressed? ITT-analyses performed?	Low risk	"The primary analysis used an ITT approach"
Free of selective reporting?	Unclear risk	Study protocol is not available
Free of other bias?	High risk	Baseline imbalance for growth hormone

Vallbona 1997

Methods	Randomised, double-blinded, placebo-controlled trial
Participants	N = 50 (magnetic treatment 29, placebo 21) Mean age: 51.5 years (magnetic treatment), 55.9 years (placebo) Gender distribution, male (%): 17% (magnetic treatment), 29% (placebo) Inclusion: diagnosis of PPS according to the criteria of Dalakas (1995), significant muscular or arthritic pain for at least 4 weeks, a trigger point or a circumscribed painful region by palpation, body weight less than 140% of predicted for age and height
Interventions	Treatment intervention: application of an active 300 to 500 Gauss magnetic device directly applied to a pain trigger point for 45 minutes Control intervention: application of placebo device
Outcomes	Measurements pre-treatment and directly post-treatment Outcome: intensity of pain felt on palpation of the active trigger point
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"an envelope....was randomly selected from a box"
Allocation concealment?	Low risk	"The manufacturer supplied us with an equal number of active and placebo devices, placed in number coded envelopes. The code numbers were not broken until all patients completed the study"
Blinding? All outcomes - patients?	Low risk	"Double-blind"; "active and placebo devices were of identical size and shape"; "the code numbers were not broken until all patients completed the study"
Blinding? All outcomes - administrators of the inter-	Low risk	"Double-blind"; "active and placebo devices were of identical size and shape"; "the

Vallbona 1997 (*Continued*)

vention?		code numbers were not broken until all patients completed the study"
Blinding? All outcomes - outcome assessors?	Low risk	"Double-blind"; "active and placebo devices were of identical size and shape"; "the code numbers were not broken until all patients completed the study"
Incomplete outcome data addressed? Missing outcome data?	Low risk	No missing outcomes
Incomplete outcome data addressed? ITT-analyses performed?	Low risk	ITT-analysis is probably done since all patients received the intervention to which they were randomised
Free of selective reporting?	High risk	Study protocol is not available. Pre-specified outcome measure (McGill Pain Questionnaire) is not reported
Free of other bias?	Low risk	

Vasconcelos 2007

Methods	Randomised, double-blinded, placebo-controlled, cross-over trial
Participants	N = 36 (phase 1: modafinil 18, placebo 18; phase 2: modafinil 18, placebo 15) Mean age: 63.1 years (modafinil first), 59.3 years (placebo first) Gender distribution, male (%): 33% (modafinil first), 39% (placebo first) Inclusion: diagnosis of PPS according to a modified version (interval $\geq$ 10 years of stable function) of the criteria of March of Dimes (2001), $\geq$ 18 years old Exclusion: no or minimal fatigue, presence of confounding medical conditions, allergic to modafinil, pregnant and breastfeeding women, patients who report pain as their dominant symptom
Interventions	Treatment intervention: a 6-week period of modafinil of 200 mg 2 times per day Control intervention: placebo Wash-out interval: 14 days
Outcomes	Measurements at baseline, and post-treatment Primary: fatigue (FSS) Secondary: fatigue (VAS, FIS), HRQoL (SF-36)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Vasconcelos 2007 (*Continued*)

Adequate sequence generation?	Low risk	"Patients were allocated to treatment using computerized block randomisation"
Allocation concealment?	Low risk	"The pharmacist formulated matching modafinil and placebo capsules, and concealed allocations from investigators by securing treatment codes."
Blinding? All outcomes - patients?	Low risk	"double-blind study" Comment: although there were more side effects experienced during modafinil treatment analysis on effectiveness of blinding provided evidence for successful blinding
Blinding? All outcomes - administrators of the intervention?	Low risk	"...concealed allocations from investigators by securing treatment codes."
Blinding? All outcomes - outcome assessors?	Low risk	"...concealed allocations from investigators by securing treatment codes."
Incomplete outcome data addressed? Missing outcome data?	High risk	Missing outcomes: modafinil first - 3/18, placebo first - 0/18 Comment: reason for missing outcome data likely related to true outcome
Incomplete outcome data addressed? ITT-analyses performed?	Low risk	Results in the ITT-sample did not differ from the per-protocol sample
Free of selective reporting?	Low risk	Study protocol available in trial register (NCT00067496): pre-specified outcomes have been reported
Free of other bias?	Low risk	Because PPS is considered a reasonably stable chronic condition and modafinil is a medicament with a temporary effect, we considered the use of a cross-over design appropriate

PPS: postpolio syndrome; VAS: visual analogue scale; FSS: Fatigue Severity Scale; CSF: cerebrospinal fluid; S-IgA: secretory immunoglobulin A; SF-36: Short Form-36 Health Survey; PASE: Physical Activity Scale for the Elderly; MFI: Multidimensional Fatigue Inventory; ITT: intention-to-treat; NHP: Nottingham Health Profile; HRQoL: health-related quality of life; BDI: Beck Depression Inventory; ADL: activities of daily living; RMI: Rivermead Mobility Index; 6-MWT: 6 Minute Walking Test; TUG: Timed Up & Go Test; IGF-1: insulin-like growth factor 1; FIS: Fatigue Impact Scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bruno 1996	No randomisation
Dean 1988	No randomisation
Dean 1991	Did not include any of our pre-specified outcome measures
Ghahari 2010	Did not meet our pre-specified criteria for PPS
Jones 1989	Did not include any of our pre-specified outcome measures
Klein 2002	Did not include a control group consisting of placebo, usual care or no treatment.
Kriz 1992	Did not meet our pre-specified criteria for PPS
Miller 1997	No full-text available
Oncu 2009	Did not include a control group consisting of placebo, usual care or no treatment
Skough 2008	Did not include a control group consisting of placebo, usual care or no treatment
Willen 2001	No randomisation

PPS: postpolio syndrome.

Characteristics of ongoing studies *[ordered by study ID]*

Koopman 2010

Trial name or title	Exercise therapy and cognitive behavioural therapy in postpoliomyelitis syndrome: effects on fatigue, activities and quality of life
Methods	Randomised, controlled trial
Participants	N = 81 Inclusion: diagnosis of PPS according to the criteria of March and Dimes (March of Dimes Foundation 2000) , severe perceived fatigue, age between 18 and 75 years, life-expectancy longer than one year, walking-ability at least indoors with or without a walking aid, ability to cycle on a cycle ergometer against a load of at least 25 Watt Exclusion: use of psychotropic drugs or other psychiatric treatment, clinical depression, disabling co-morbidity, respiratory insufficiency or assisted ventilation, cognitive impairment, insufficient mastery of the Dutch language, pregnancy

Koopman 2010 (*Continued*)

Interventions	(1) Exercise therapy and usual care versus (2) cognitive behavioural therapy and usual care versus (3) usual care only
Outcomes	Measurements at baseline, at discharge from the program, and at 3 and 6 months follow-up Primary outcomes: Short-Form Health Survey (SF-36), Sickness Impact Profile; domains mobility range, mobility control, social behavior, Checklist Individual Strength; domain fatigue Secondary outcomes: pain, psychological well-being, physical activity in daily life, perceived participation, illness cognitions, coping, perceived control or self-efficacy, cost-effectiveness
Starting date	January 2009
Contact information	F.S. Koopman, University of Amsterdam, Academic Medical Center, Department of Rehabilitation, PO Box 22660, 1100 DD Amsterdam, The Netherlands, E-mail: S.Koopman@amc.uva.nl
Notes	Completion anticipated February 2012

PPS: postpolio syndrome.

DATA AND ANALYSES

Comparison 1. Modafinil versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Difference (modafinil - placebo) in activity limitations - SF-36 PF (range 0 to 100)	1		Mean Difference (Fixed, 95% CI)	1.28 [-3.56, 6.12]
2 Difference (modafinil - placebo) in fatigue - PFS (scores normalized to that at baseline, %)	1		Mean Difference (Fixed, 95% CI)	12.0 [4.16, 19.84]
3 Difference (modafinil - placebo) in fatigue - FSS (range 1 to 7)	1		Mean Difference (Fixed, 95% CI)	0.39 [-0.24, 1.02]
4 Difference (modafinil - placebo) in fatigue - VAS (0 to 10 cm)	1		Mean Difference (Fixed, 95% CI)	-0.01 [-0.93, 0.91]
5 Difference (modafinil - placebo) in fatigue - FIS (range 0 to 160)	1		Mean Difference (Fixed, 95% CI)	-3.32 [-15.22, 8.58]
6 Difference (modafinil - placebo) in pain - SF-36 BP (range 0 to 100)	1		Mean Difference (Fixed, 95% CI)	1.21 [-7.77, 10.19]

Comparison 2. IVIG versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in activity limitations-SF-36 PCS (range 0 to 100)	1	135	Mean Difference (IV, Fixed, 95% CI)	2.3 [-0.35, 4.95]
2 Change in muscle strength - % change in isometric strength of polio affected muscle	1	135	Mean Difference (IV, Fixed, 95% CI)	8.6 [2.81, 14.39]
3 Muscle strength 3 months post-treatment - isometric strength right elbow flexors (Nm)	1	20	Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Muscle strength 3 months post-treatment - isometric strength left elbow flexors (Nm)	1	20	Mean Difference (IV, Fixed, 95% CI)	0.30 [-13.31, 13.91]
5 Muscle strength 3 months post-treatment - isometric strength right knee extensors (Nm)	1	20	Mean Difference (IV, Fixed, 95% CI)	12.90 [-29.83, 55.63]

6 Muscle strength 3 months post-treatment - isometric strength left knee extensors (Nm)	1	20	Mean Difference (IV, Fixed, 95% CI)	3.60 [-44.79, 51.99]
7 Change in fatigue - MFI general fatigue (range 4 to 20)	1	130	Mean Difference (IV, Fixed, 95% CI)	Not estimable
8 Fatigue 3 months post-treatment - FSS (range 1 to 7)	1	20	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.87, 0.67]
9 Pain - VAS (range 0 to 100 mm)	2	153	Mean Difference (IV, Random, 95% CI)	-15.39 [-45.16, 14.38]
9.1 Change in pain	1	133	Mean Difference (IV, Random, 95% CI)	-1.5 [-6.60, 3.60]
9.2 Pain 3 months post-treatment	1	20	Mean Difference (IV, Random, 95% CI)	-32.0 [-50.59, -13.41]
10 Pain 3 months post-treatment - PDI (number of marked areas)	1	20	Mean Difference (IV, Fixed, 95% CI)	-6.70 [-23.63, 10.23]

Comparison 3. Pyridostigmine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in activity limitations - SF-36 PF (range 0 to 100)	1	124	Mean Difference (IV, Fixed, 95% CI)	2.1 [-3.64, 7.84]
2 Change in muscle strength - very weak muscles, % change in isometric strength	1	65	Mean Difference (IV, Fixed, 95% CI)	33.9 [-5.49, 73.29]
3 Change in muscle strength - weak muscles, % change in isometric strength	1	114	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-11.75, 8.15]
4 Change in muscle strength - relative strong muscles, % improvement in isometric strength	1	117	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-4.22, 3.62]
5 Change in muscle strength - isometric muscle strength quadriceps (Nm)	1	62	Mean Difference (IV, Fixed, 95% CI)	6.70 [-2.19, 15.59]
6 Change in muscle endurance - isometric muscle fatigability quadriceps ($MF_{0\text{-}5s}$-$MF_{25\text{-}30s}$)	1	52	Mean Difference (IV, Fixed, 95% CI)	-0.7 [-2.52, 1.12]
7 Change in fatigue - FSS (range 1 to 7)	2	186	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.34, 0.21]
8 Change in fatigue - HFSS (range 0 to 4)	1	115	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.17, 0.31]
9 Change in fatigue - NHP-energy (range 0 to 100)	1	62	Mean Difference (IV, Fixed, 95% CI)	1.10 [-16.24, 18.44]
10 Change in pain - SF-36 BP (range 0 to 100)	1	124	Mean Difference (IV, Fixed, 95% CI)	-2.1 [-9.16, 4.96]

Comparison 4. Lamotrigine versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Activity limitations post-treatment - NHP PM (range 0 to 100)	1	30	Mean Difference (IV, Fixed, 95% CI)	-23.7 [-35.35, -12.05]
2 Fatigue post-treatment - FSS (range 1 to 7)	1	30	Mean Difference (IV, Fixed, 95% CI)	-1.4 [-2.26, -0.54]
3 Fatigue post-treatment - VAS (range 0 to 10 cm)	1	30	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-3.30, 1.30]
4 Fatigue post-treatment - NHP-energy (range 0 to 100)	1	30	Mean Difference (IV, Fixed, 95% CI)	-33.30 [-53.13, -13.47]
5 Pain post-treatment - VAS (range 0 to 10 cm)	1	30	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-4.36, -1.24]
6 Pain post-treatment - NHP-pain (range 0 to 100)	1	30	Mean Difference (IV, Fixed, 95% CI)	-30.50 [-42.72, -18.28]

Comparison 5. Amantadine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fatigue - number of patients improved	1	25	Risk Ratio (M-H, Fixed, 95% CI)	2.55 [0.81, 7.95]

Comparison 6. Prednisone versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fatigue - number of patients improved or not changed	1	12	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.75, 1.70]

Comparison 7. Muscle strengthening versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in muscle strength - % change in isometric strength of thenar muscle	1	10	Mean Difference (IV, Fixed, 95% CI)	39.0 [6.12, 71.88]

Comparison 8. Rehabilitation in cold climate versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Activity limitations 3 months post-treatment - Sunnaas ADL-index (range 0 to 36)	1	53	Mean Difference (IV, Fixed, 95% CI)	-2.70 [-4.53, -0.87]
2 Activity limitations 6 months post-treatment - Sunnaas ADL-index (range 0 to 36)	1	53	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-4.73, -1.07]
3 Acitivity limitations 3 months post-treatment - Rivermead Mobility Index (range 0 to 15)	1	53	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-2.93, -0.07]
4 Acitivity limitations 6 months post-treatment - Rivermead Mobility Index (range 0 to 15)	1	53	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-3.19, -0.41]
5 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, right hand (% pred)	1	51	Mean Difference (IV, Fixed, 95% CI)	-5.00 [-21.82, 11.82]
6 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, left hand (% pred)	1	51	Mean Difference (IV, Fixed, 95% CI)	5.0 [-11.21, 21.21]
7 Fatigue 3 months post-treatment - FSS (range 1 to 7)	1	53	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.47, 0.67]
8 Pain 3 months post-treatment - VAS (range 0 to 100 mm)	1	55	Mean Difference (IV, Fixed, 95% CI)	11.00 [-0.98, 22.98]

Comparison 9. Rehabilitation in warm climate versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Activity limitations 3 months post-treatment - Sunnaas ADL-index (range 0 to 36)	1	57	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-3.47, 0.07]
2 Activity limitations 3 months post-treatment - Rivermead Mobility Index (range 0 to 15)	1	57	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.28, 0.48]
3 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, right hand (% pred)	1	54	Mean Difference (IV, Fixed, 95% CI)	2.0 [-15.15, 19.15]
4 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, left hand (% pred)	1	55	Mean Difference (IV, Fixed, 95% CI)	6.0 [-9.10, 21.10]
5 Fatigue 3 months post-treatment - FSS (range 1 to 7)	1	57	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.02, 0.22]
6 Pain 3 months post-treatment - VAS (range 0 to 100 mm)	1	58	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-16.88, 6.88]

Comparison 10. Static magnetic fields versus placebo

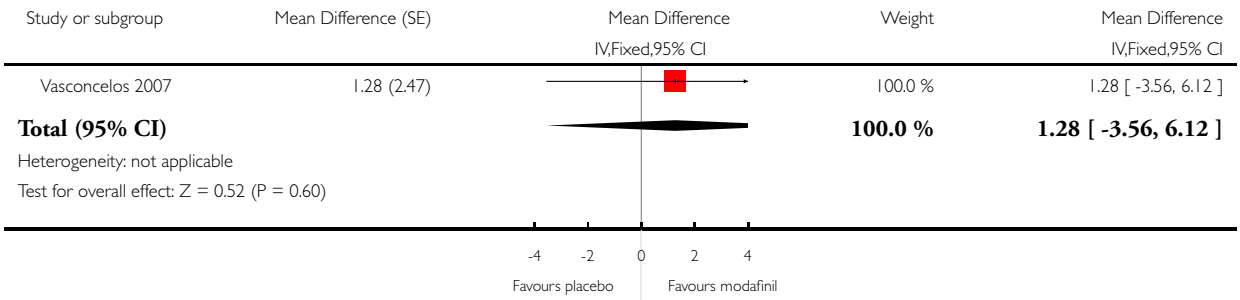
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in pain - intensity of pain felt on palpation of active trigger point (range 1 to 10)	1	50	Mean Difference (IV, Fixed, 95% CI)	4.1 [2.75, 5.45]

Analysis 1.1. Comparison 1 Modafinil versus placebo, Outcome 1 Difference (modafinil - placebo) in activity limitations - SF-36 PF (range 0 to 100).

Review: Treatment for postpolio syndrome

Comparison: 1 Modafinil versus placebo

Outcome: 1 Difference (modafinil - placebo) in activity limitations - SF-36 PF (range 0 to 100)

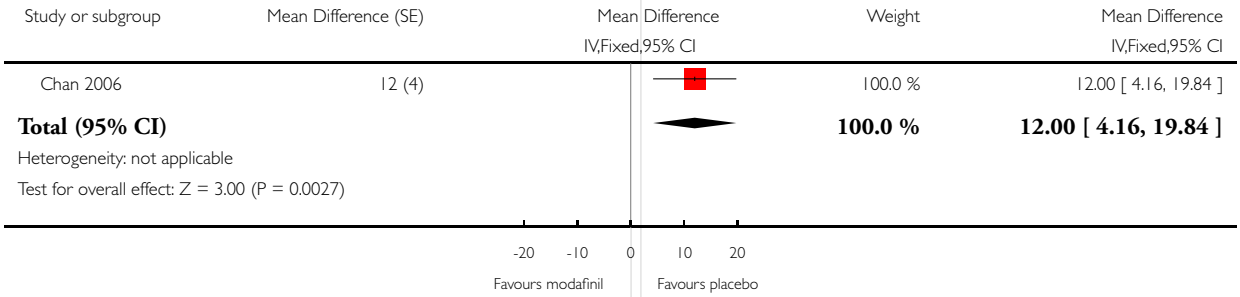


Analysis 1.2. Comparison 1 Modafinil versus placebo, Outcome 2 Difference (modafinil - placebo) in fatigue - PFS (scores normalized to that at baseline, %).

Review: Treatment for postpolio syndrome

Comparison: 1 Modafinil versus placebo

Outcome: 2 Difference (modafinil - placebo) in fatigue - PFS (scores normalized to that at baseline, %)

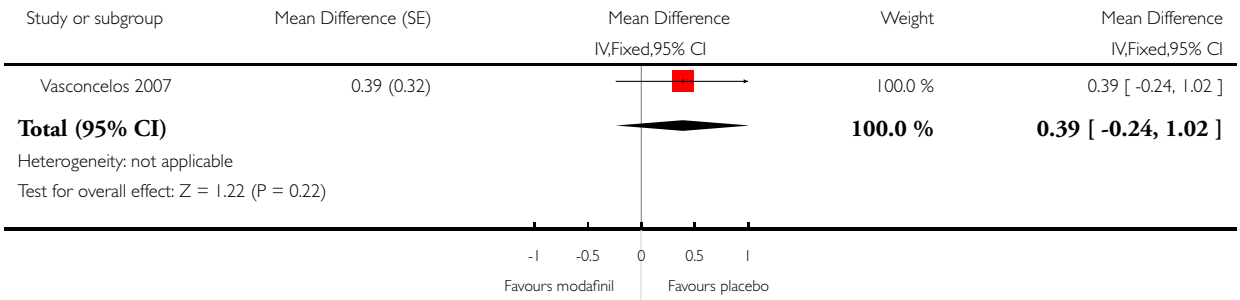


Analysis 1.3. Comparison 1 Modafinil versus placebo, Outcome 3 Difference (modafinil - placebo) in fatigue - FSS (range 1 to 7).

Review: Treatment for postpolio syndrome

Comparison: 1 Modafinil versus placebo

Outcome: 3 Difference (modafinil - placebo) in fatigue - FSS (range 1 to 7)

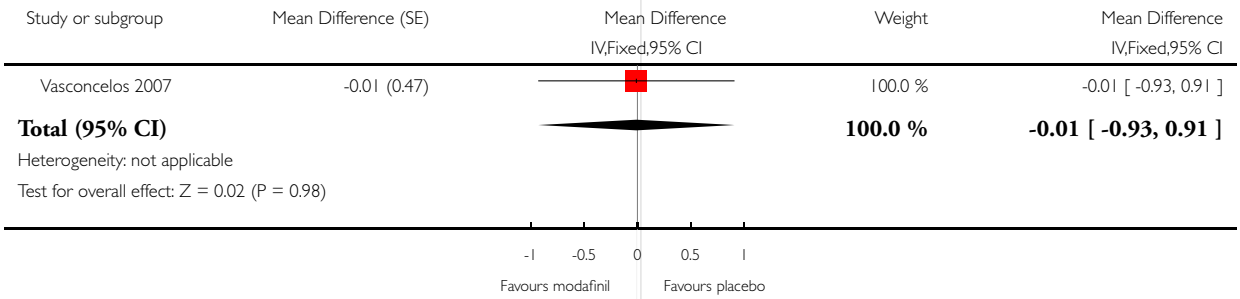


Analysis 1.4. Comparison 1 Modafinil versus placebo, Outcome 4 Difference (modafinil - placebo) in fatigue - VAS (0 to 10 cm).

Review: Treatment for postpolio syndrome

Comparison: 1 Modafinil versus placebo

Outcome: 4 Difference (modafinil - placebo) in fatigue - VAS (0 to 10 cm)

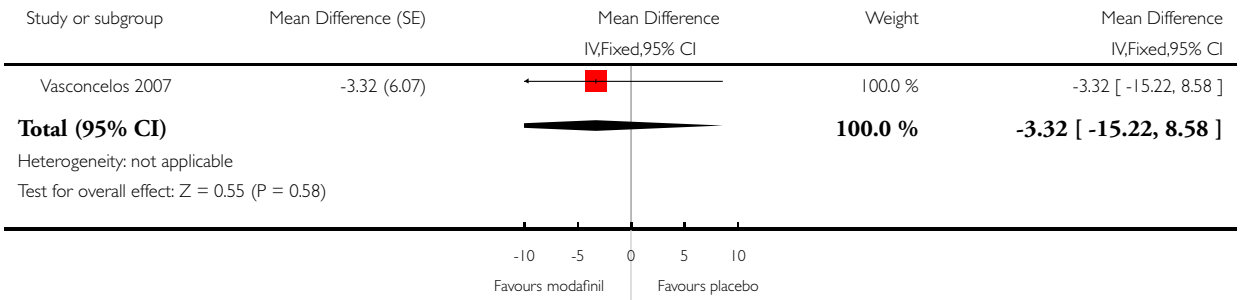


Analysis 1.5. Comparison 1 Modafinil versus placebo, Outcome 5 Difference (modafinil - placebo) in fatigue - FIS (range 0 to 160).

Review: Treatment for postpolio syndrome

Comparison: 1 Modafinil versus placebo

Outcome: 5 Difference (modafinil - placebo) in fatigue - FIS (range 0 to 160)

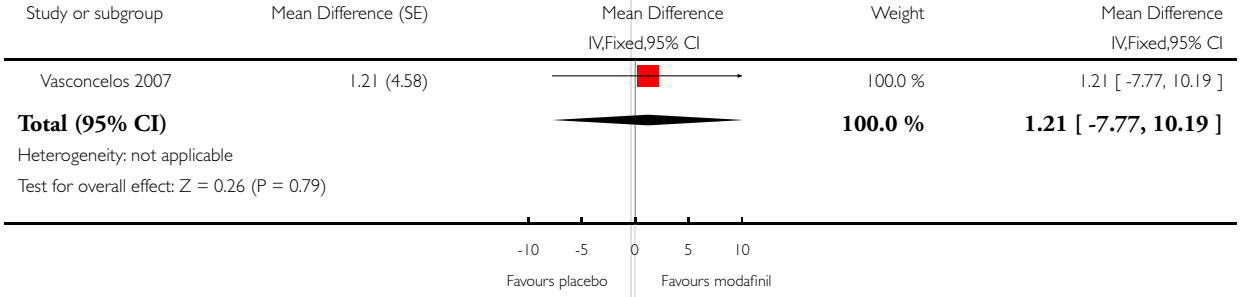


Analysis 1.6. Comparison 1 Modafinil versus placebo, Outcome 6 Difference (modafinil - placebo) in pain - SF-36 BP (range 0 to 100).

Review: Treatment for postpolio syndrome

Comparison: 1 Modafinil versus placebo

Outcome: 6 Difference (modafinil - placebo) in pain - SF-36 BP (range 0 to 100)



Analysis 2.1. Comparison 2 IVIG versus placebo, Outcome 1 Change in activity limitations- SF-36 PCS (range 0 to 100).

Review: Treatment for postpolio syndrome

Comparison: 2 IVIG versus placebo

Outcome: 1 Change in activity limitations- SF-36 PCS (range 0 to 100)

Study or subgroup	IVIG N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gonzalez 2006	67	1.5 (8.2)	68	-0.8 (7.5)		100.0 %	2.30 [-0.35, 4.95]
Total (95% CI)	**67**		**68**			**100.0 %**	**2.30 [-0.35, 4.95]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.70 (P = 0.089)

Analysis 2.2. Comparison 2 IVIG versus placebo, Outcome 2 Change in muscle strength - % change in isometric strength of polio affected muscle.

Review: Treatment for postpolio syndrome

Comparison: 2 IVIG versus placebo

Outcome: 2 Change in muscle strength - % change in isometric strength of polio affected muscle

Study or subgroup	IVIG N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gonzalez 2006	67	2.3 (16.8)	68	-6.3 (17.5)		100.0 %	8.60 [2.81, 14.39]
Total (95% CI)	**67**		**68**			**100.0 %**	**8.60 [2.81, 14.39]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.91 (P = 0.0036)

Analysis 2.3. Comparison 2 IVIG versus placebo, Outcome 3 Muscle strength 3 months post-treatment - isometric strength right elbow flexors (Nm).

Review: Treatment for postpolio syndrome

Comparison: 2 IVIG versus placebo

Outcome: 3 Muscle strength 3 months post-treatment - isometric strength right elbow flexors (Nm)

Study or subgroup	IVIG N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Farbu 2007	10	26.7 (6.3)	10	26.7 (14.1)		100.0 %	0.0 [-9.57, 9.57]
Total (95% CI)	**10**		**10**			**100.0 %**	**0.0 [-9.57, 9.57]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Analysis 2.4. Comparison 2 IVIG versus placebo, Outcome 4 Muscle strength 3 months post-treatment - isometric strength left elbow flexors (Nm).

Review: Treatment for postpolio syndrome

Comparison: 2 IVIG versus placebo

Outcome: 4 Muscle strength 3 months post-treatment - isometric strength left elbow flexors (Nm)

Study or subgroup	IVIG N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Farbu 2007	10	27.3 (11)	10	27 (19)		100.0 %	0.30 [-13.31, 13.91]
Total (95% CI)	**10**		**10**			**100.0 %**	**0.30 [-13.31, 13.91]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.04 (P = 0.97)

Analysis 2.5. Comparison 2 IVIG versus placebo, Outcome 5 Muscle strength 3 months post-treatment - isometric strength right knee extensors (Nm).

Review: Treatment for postpolio syndrome

Comparison: 2 IVIG versus placebo

Outcome: 5 Muscle strength 3 months post-treatment - isometric strength right knee extensors (Nm)

Study or subgroup	IVIG N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Farbu 2007	10	75.7 (36.8)	10	62.8 (58.3)		100.0 %	12.90 [-29.83, 55.63]
Total (95% CI)	**10**		**10**			**100.0 %**	**12.90 [-29.83, 55.63]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.59 (P = 0.55)

Analysis 2.6. Comparison 2 IVIG versus placebo, Outcome 6 Muscle strength 3 months post-treatment - isometric strength left knee extensors (Nm).

Review: Treatment for postpolio syndrome

Comparison: 2 IVIG versus placebo

Outcome: 6 Muscle strength 3 months post-treatment - isometric strength left knee extensors (Nm)

Study or subgroup	IVIG N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Farbu 2007	10	70.8 (43.1)	10	67.2 (65.1)		100.0 %	3.60 [-44.79, 51.99]
Total (95% CI)	**10**		**10**			**100.0 %**	**3.60 [-44.79, 51.99]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.15 (P = 0.88)

Analysis 2.7. Comparison 2 IVIG versus placebo, Outcome 7 Change in fatigue - MFI general fatigue (range 4 to 20).

Review: Treatment for postpolio syndrome

Comparison: 2 IVIG versus placebo

Outcome: 7 Change in fatigue - MFI general fatigue (range 4 to 20)

Study or subgroup	IVIG N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gonzalez 2006	65	1 (3.7)	65	1 (2.2)		100.0 %	0.0 [-1.05, 1.05]
Total (95% CI)	**65**		**65**			**100.0 %**	**0.0 [-1.05, 1.05]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P = 1.0)

Analysis 2.8. Comparison 2 IVIG versus placebo, Outcome 8 Fatigue 3 months post-treatment - FSS (range 1 to 7).

Review: Treatment for postpolio syndrome

Comparison: 2 IVIG versus placebo

Outcome: 8 Fatigue 3 months post-treatment - FSS (range 1 to 7)

Study or subgroup	IVIG N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Farbu 2007	10	4.5 (1.4)	10	5.1 (1.5)		100.0 %	-0.60 [-1.87, 0.67]
Total (95% CI)	**10**		**10**			**100.0 %**	**-0.60 [-1.87, 0.67]**

Heterogeneity: not applicable

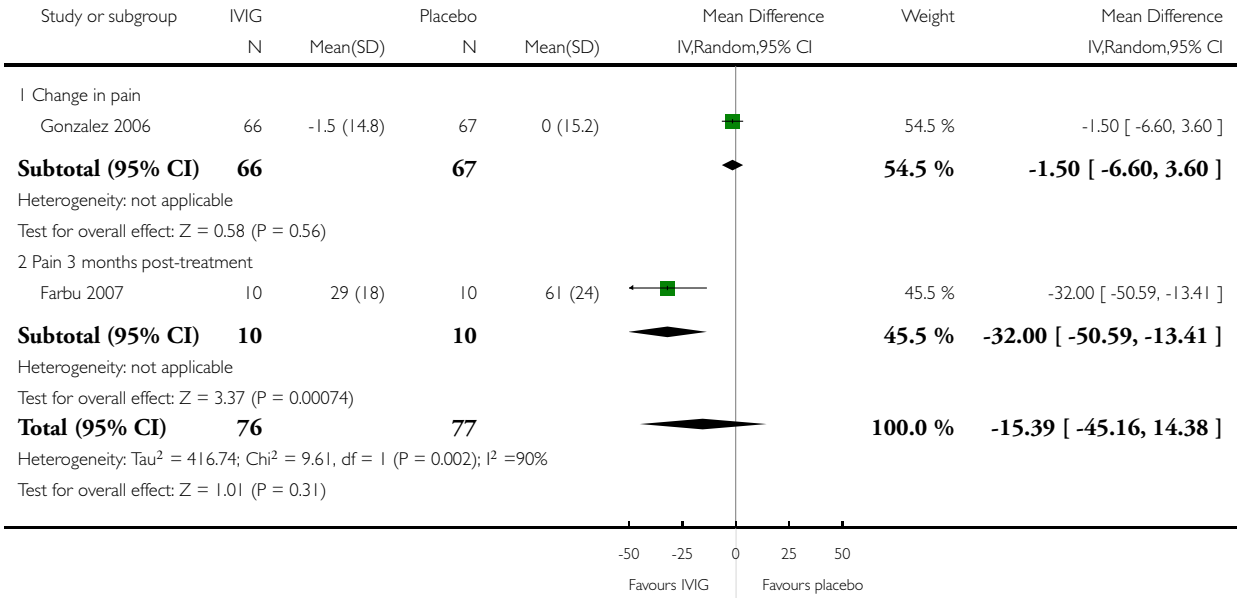
Test for overall effect: Z = 0.92 (P = 0.36)

Analysis 2.9. Comparison 2 IVIG versus placebo, Outcome 9 Pain - VAS (range 0 to 100 mm).

Review: Treatment for postpolio syndrome

Comparison: 2 IVIG versus placebo

Outcome: 9 Pain - VAS (range 0 to 100 mm)

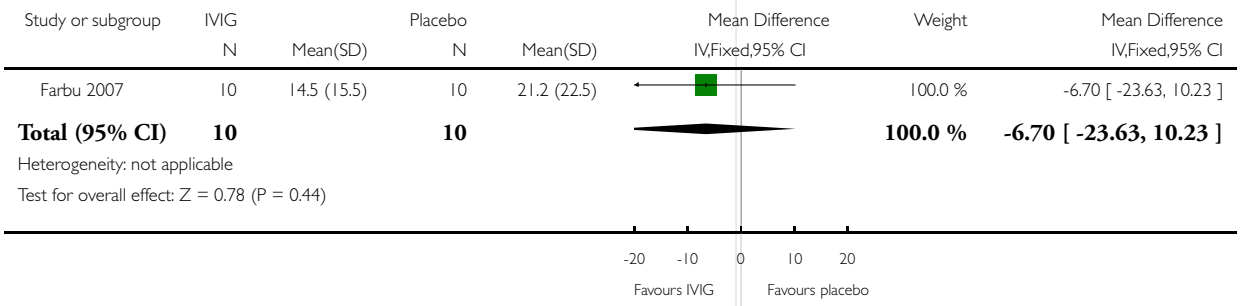


Analysis 2.10. Comparison 2 IVIG versus placebo, Outcome 10 Pain 3 months post-treatment - PDI (number of marked areas).

Review: Treatment for postpolio syndrome

Comparison: 2 IVIG versus placebo

Outcome: 10 Pain 3 months post-treatment - PDI (number of marked areas)



Analysis 3.1. Comparison 3 Pyridostigmine versus placebo, Outcome 1 Change in activity limitations - SF-36 PF (range 0 to 100).

Review: Treatment for postpolio syndrome

Comparison: 3 Pyridostigmine versus placebo

Outcome: 1 Change in activity limitations - SF-36 PF (range 0 to 100)

Study or subgroup	Pyridostigmine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Trojan 1999	63	3.2 (17.9)	61	1.1 (14.6)		100.0 %	2.10 [-3.64, 7.84]
Total (95% CI)	**63**		**61**			**100.0 %**	**2.10 [-3.64, 7.84]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.72 (P = 0.47)

Analysis 3.2. Comparison 3 Pyridostigmine versus placebo, Outcome 2 Change in muscle strength - very weak muscles, % change in isometric strength.

Review: Treatment for postpolio syndrome

Comparison: 3 Pyridostigmine versus placebo

Outcome: 2 Change in muscle strength - very weak muscles, % change in isometric strength

Study or subgroup	Pyridostigmine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Trojan 1999	36	41.8 (108.5)	29	7.9 (47.2)		100.0 %	33.90 [-5.49, 73.29]
Total (95% CI)	**36**		**29**			**100.0 %**	**33.90 [-5.49, 73.29]**

Heterogeneity: not applicable

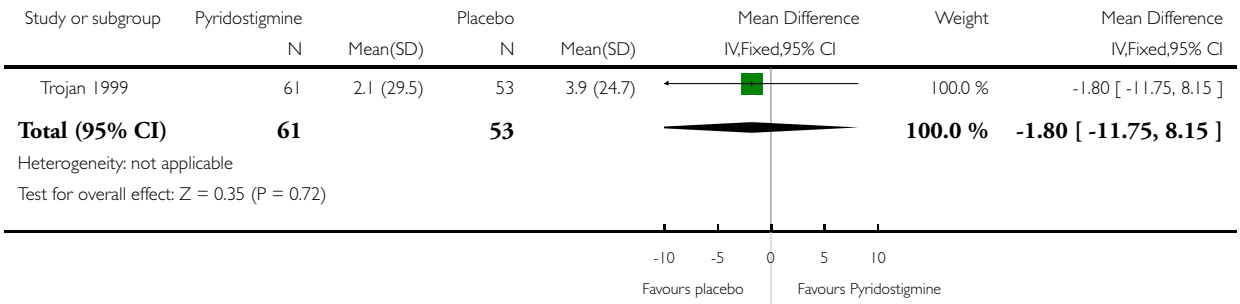
Test for overall effect: Z = 1.69 (P = 0.092)

Analysis 3.3. Comparison 3 Pyridostigmine versus placebo, Outcome 3 Change in muscle strength - weak muscles, % change in isometric strength.

Review: Treatment for postpolio syndrome

Comparison: 3 Pyridostigmine versus placebo

Outcome: 3 Change in muscle strength - weak muscles, % change in isometric strength

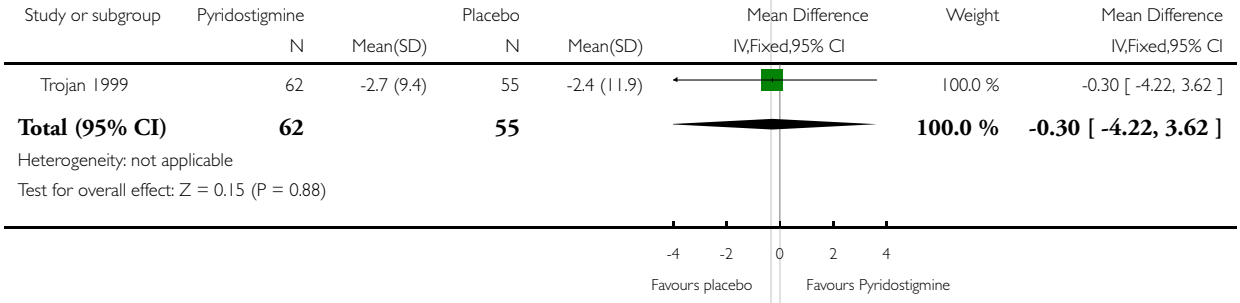


Analysis 3.4. Comparison 3 Pyridostigmine versus placebo, Outcome 4 Change in muscle strength - relative strong muscles, % improvement in isometric strength.

Review: Treatment for postpolio syndrome

Comparison: 3 Pyridostigmine versus placebo

Outcome: 4 Change in muscle strength - relative strong muscles, % improvement in isometric strength



Analysis 3.5. Comparison 3 Pyridostigmine versus placebo, Outcome 5 Change in muscle strength - isometric muscle strength quadriceps (Nm).

Review: Treatment for postpolio syndrome

Comparison: 3 Pyridostigmine versus placebo

Outcome: 5 Change in muscle strength - isometric muscle strength quadriceps (Nm)

Study or subgroup	Pyridostigmine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Horemans 2003	31	12.7 (21.4)	31	6 (13.4)		100.0 %	6.70 [-2.19, 15.59]
Total (95% CI)	**31**		**31**			**100.0 %**	**6.70 [-2.19, 15.59]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.48 (P = 0.14)

Analysis 3.6. Comparison 3 Pyridostigmine versus placebo, Outcome 6 Change in muscle endurance - isometric muscle fatigability quadriceps (MF_{0-5s} - MF_{25-30s}).

Review: Treatment for postpolio syndrome

Comparison: 3 Pyridostigmine versus placebo

Outcome: 6 Change in muscle endurance - isometric muscle fatigability quadriceps (MF_{0-5s} - MF_{25-30s})

Study or subgroup	Pyridostigmine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Horemans 2003	26	-0.9 (3.4)	26	-0.2 (3.3)		100.0 %	-0.70 [-2.52, 1.12]
Total (95% CI)	**26**		**26**			**100.0 %**	**-0.70 [-2.52, 1.12]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.75 (P = 0.45)

Analysis 3.7. Comparison 3 Pyridostigmine versus placebo, Outcome 7 Change in fatigue - FSS (range 1 to 7).

Review: Treatment for postpolio syndrome

Comparison: 3 Pyridostigmine versus placebo

Outcome: 7 Change in fatigue - FSS (range 1 to 7)

Study or subgroup	Pyridostigmine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Horemans 2003	31	0.6 (0.9)	31	0.4 (0.9)		37.0 %	0.20 [-0.25, 0.65]
Trojan 1999	63	0.05 (0.77)	61	0.27 (1.14)		63.0 %	-0.22 [-0.56, 0.12]
Total (95% CI)	**94**		**92**			**100.0 %**	**-0.06 [-0.34, 0.21]**

Heterogeneity: Chi^2 = 2.13, df = 1 (P = 0.14); I^2 =53%

Test for overall effect: Z = 0.46 (P = 0.64)

Analysis 3.8. Comparison 3 Pyridostigmine versus placebo, Outcome 8 Change in fatigue - HFSS (range 0 to 4).

Review: Treatment for postpolio syndrome

Comparison: 3 Pyridostigmine versus placebo

Outcome: 8 Change in fatigue - HFSS (range 0 to 4)

Study or subgroup	Pyridostigmine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Trojan 1999	58	0.27 (0.65)	57	0.2 (0.65)		100.0 %	0.07 [-0.17, 0.31]
Total (95% CI)	**58**		**57**			**100.0 %**	**0.07 [-0.17, 0.31]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.58 (P = 0.56)

Analysis 3.9. Comparison 3 Pyridostigmine versus placebo, Outcome 9 Change in fatigue - NHP-energy (range 0 to 100).

Review: Treatment for postpolio syndrome

Comparison: 3 Pyridostigmine versus placebo

Outcome: 9 Change in fatigue - NHP-energy (range 0 to 100)

Study or subgroup	Pyridostigmine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Horemans 2003	31	18.3 (36.4)	31	17.2 (33.2)		100.0 %	1.10 [-16.24, 18.44]
Total (95% CI)	**31**		**31**			**100.0 %**	**1.10 [-16.24, 18.44]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.12 (P = 0.90)

Analysis 3.10. Comparison 3 Pyridostigmine versus placebo, Outcome 10 Change in pain - SF-36 BP (range 0 to 100).

Review: Treatment for postpolio syndrome

Comparison: 3 Pyridostigmine versus placebo

Outcome: 10 Change in pain - SF-36 BP (range 0 to 100)

Study or subgroup	Pyridostigmine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Trojan 1999	63	0.6 (18.8)	61	2.7 (21.2)		100.0 %	-2.10 [-9.16, 4.96]
Total (95% CI)	**63**		**61**			**100.0 %**	**-2.10 [-9.16, 4.96]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.58 (P = 0.56)

Analysis 4.1. Comparison 4 Lamotrigine versus control, Outcome 1 Activity limitations post-treatment - NHP PM (range 0 to 100).

Review: Treatment for postpolio syndrome

Comparison: 4 Lamotrigine versus control

Outcome: 1 Activity limitations post-treatment - NHP PM (range 0 to 100)

Study or subgroup	Lamotrigine N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
On 2005	15	14.7 (13.3)	15	38.4 (18.8)		100.0 %	-23.70 [-35.35, -12.05]
Total (95% CI)	**15**		**15**			**100.0 %**	**-23.70 [-35.35, -12.05]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.99 (P = 0.000067)

Analysis 4.2. Comparison 4 Lamotrigine versus control, Outcome 2 Fatigue post-treatment - FSS (range 1 to 7).

Review: Treatment for postpolio syndrome

Comparison: 4 Lamotrigine versus control

Outcome: 2 Fatigue post-treatment - FSS (range 1 to 7)

Study or subgroup	Lamotrigine N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
On 2005	15	2.5 (1.1)	15	3.9 (1.3)		100.0 %	-1.40 [-2.26, -0.54]
Total (95% CI)	**15**		**15**			**100.0 %**	**-1.40 [-2.26, -0.54]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.18 (P = 0.0015)

Analysis 4.3. Comparison 4 Lamotrigine versus control, Outcome 3 Fatigue post-treatment - VAS (range 0 to 10 cm).

Review: Treatment for postpolio syndrome

Comparison: 4 Lamotrigine versus control

Outcome: 3 Fatigue post-treatment - VAS (range 0 to 10 cm)

Study or subgroup	Lamotrigine N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
On 2005	15	3 (2.9)	15	4 (3.5)		100.0 %	-1.00 [-3.30, 1.30]
Total (95% CI)	**15**		**15**			**100.0 %**	**-1.00 [-3.30, 1.30]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.85 (P = 0.39)

Analysis 4.4. Comparison 4 Lamotrigine versus control, Outcome 4 Fatigue post-treatment - NHP-energy (range 0 to 100).

Review: Treatment for postpolio syndrome

Comparison: 4 Lamotrigine versus control

Outcome: 4 Fatigue post-treatment - NHP-energy (range 0 to 100)

Study or subgroup	Lamotrigine N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
On 2005	15	2.4 (6.7)	15	35.7 (38.6)		100.0 %	-33.30 [-53.13, -13.47]
Total (95% CI)	**15**		**15**			**100.0 %**	**-33.30 [-53.13, -13.47]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.29 (P = 0.00099)

Analysis 4.5. Comparison 4 Lamotrigine versus control, Outcome 5 Pain post-treatment - VAS (range 0 to 10 cm).

Review: Treatment for postpolio syndrome

Comparison: 4 Lamotrigine versus control

Outcome: 5 Pain post-treatment - VAS (range 0 to 10 cm)

Study or subgroup	Lamotrigine N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
On 2005	15	1.6 (1.5)	15	4.4 (2.7)		100.0 %	-2.80 [-4.36, -1.24]
Total (95% CI)	**15**		**15**			**100.0 %**	**-2.80 [-4.36, -1.24]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.51 (P = 0.00045)

Analysis 4.6. Comparison 4 Lamotrigine versus control, Outcome 6 Pain post-treatment - NHP-pain (range 0 to 100).

Review: Treatment for postpolio syndrome

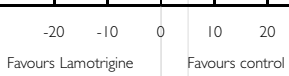
Comparison: 4 Lamotrigine versus control

Outcome: 6 Pain post-treatment - NHP-pain (range 0 to 100)

Study or subgroup	Lamotrigine N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
On 2005	15	7.9 (14.1)	15	38.4 (19.6)		100.0 %	-30.50 [-42.72, -18.28]
Total (95% CI)	**15**		**15**			**100.0 %**	**-30.50 [-42.72, -18.28]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.89 (P < 0.00001)

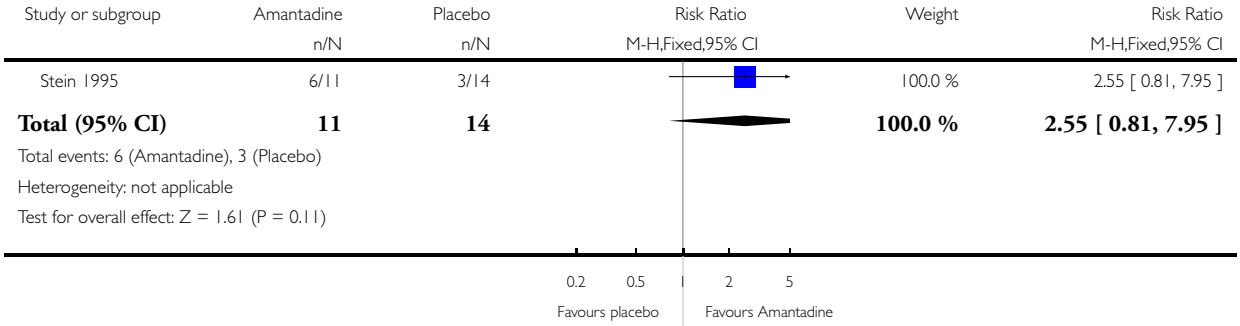


Analysis 5.1. Comparison 5 Amantadine versus placebo, Outcome 1 Fatigue - number of patients improved.

Review: Treatment for postpolio syndrome

Comparison: 5 Amantadine versus placebo

Outcome: 1 Fatigue - number of patients improved

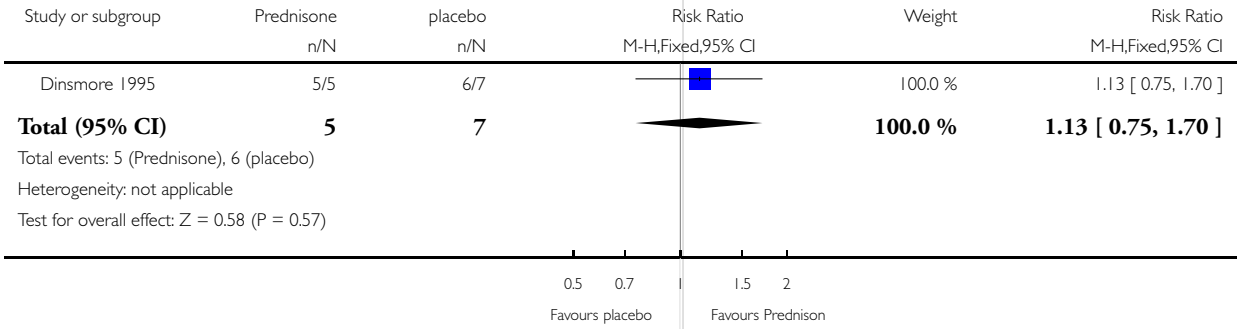


Analysis 6.1. Comparison 6 Prednisone versus placebo, Outcome 1 Fatigue - number of patients improved or not changed.

Review: Treatment for postpolio syndrome

Comparison: 6 Prednisone versus placebo

Outcome: 1 Fatigue - number of patients improved or not changed

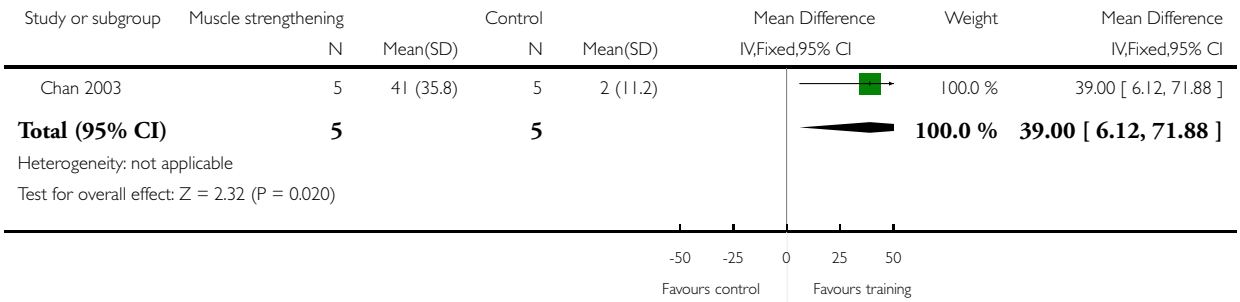


Analysis 7.1. Comparison 7 Muscle strengthening versus control, Outcome 1 Change in muscle strength - % change in isometric strength of thenar muscle.

Review: Treatment for postpolio syndrome

Comparison: 7 Muscle strengthening versus control

Outcome: 1 Change in muscle strength - % change in isometric strength of thenar muscle

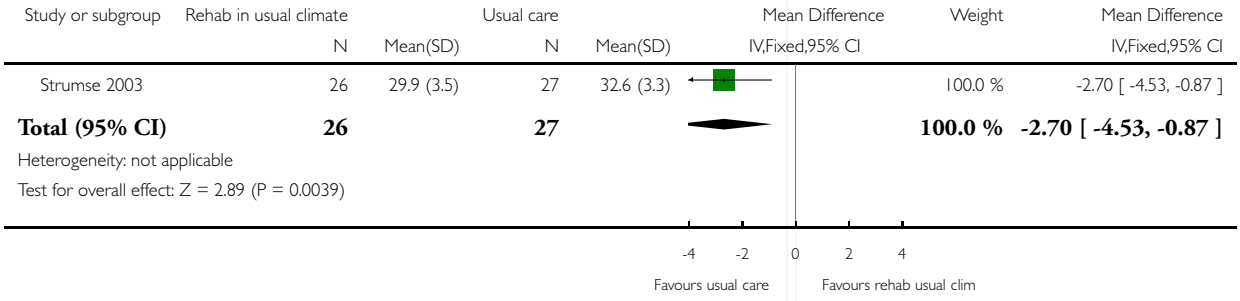


Analysis 8.1. Comparison 8 Rehabilitation in cold climate versus usual care, Outcome 1 Activity limitations 3 months post-treatment - Sunnaas ADL-index (range 0 to 36).

Review: Treatment for postpolio syndrome

Comparison: 8 Rehabilitation in cold climate versus usual care

Outcome: 1 Activity limitations 3 months post-treatment - Sunnaas ADL-index (range 0 to 36)



Analysis 8.2. Comparison 8 Rehabilitation in cold climate versus usual care, Outcome 2 Activity limitations 6 months post-treatment - Sunnaas ADL-index (range 0 to 36).

Review: Treatment for postpolio syndrome

Comparison: 8 Rehabilitation in cold climate versus usual care

Outcome: 2 Activity limitations 6 months post-treatment - Sunnaas ADL-index (range 0 to 36)

Study or subgroup	Rehab in usual climate N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Strumse 2003	27	29.5 (3.5)	26	32.4 (3.3)		100.0 %	-2.90 [-4.73, -1.07]
Total (95% CI)	**27**		**26**			**100.0 %**	**-2.90 [-4.73, -1.07]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.10 (P = 0.0019)

Analysis 8.3. Comparison 8 Rehabilitation in cold climate versus usual care, Outcome 3 Acitivity limitations 3 months post-treatment - Rivermead Mobility Index (range 0 to 15).

Review: Treatment for postpolio syndrome

Comparison: 8 Rehabilitation in cold climate versus usual care

Outcome: 3 Acitivity limitations 3 months post-treatment - Rivermead Mobility Index (range 0 to 15)

Study or subgroup	Rehab in usual climate N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Strumse 2003	26	11.7 (2.8)	27	13.2 (2.5)		100.0 %	-1.50 [-2.93, -0.07]
Total (95% CI)	**26**		**27**			**100.0 %**	**-1.50 [-2.93, -0.07]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.05 (P = 0.040)

Analysis 8.4. Comparison 8 Rehabilitation in cold climate versus usual care, Outcome 4 Acitivity limitations 6 months post-treatment - Rivermead Mobility Index (range 0 to 15).

Review: Treatment for postpolio syndrome

Comparison: 8 Rehabilitation in cold climate versus usual care

Outcome: 4 Acitivity limitations 6 months post-treatment - Rivermead Mobility Index (range 0 to 15)

Study or subgroup	Rehab in usual climate N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Strumse 2003	27	11.7 (3)	26	13.5 (2.1)		100.0 %	-1.80 [-3.19, -0.41]
Total (95% CI)	**27**		**26**			**100.0 %**	**-1.80 [-3.19, -0.41]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.54 (P = 0.011)

Analysis 8.5. Comparison 8 Rehabilitation in cold climate versus usual care, Outcome 5 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, right hand (% pred).

Review: Treatment for postpolio syndrome

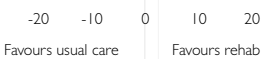
Comparison: 8 Rehabilitation in cold climate versus usual care

Outcome: 5 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, right hand (% pred)

Study or subgroup	Rehab in usual climate N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Strumse 2003	25	61 (27)	26	66 (34)		100.0 %	-5.00 [-21.82, 11.82]
Total (95% CI)	**25**		**26**			**100.0 %**	**-5.00 [-21.82, 11.82]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.58 (P = 0.56)

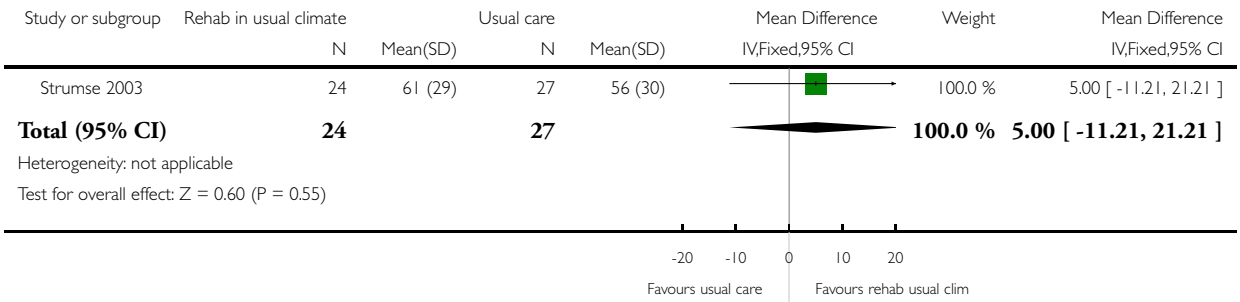


Analysis 8.6. Comparison 8 Rehabilitation in cold climate versus usual care, Outcome 6 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, left hand (% pred).

Review: Treatment for postpolio syndrome

Comparison: 8 Rehabilitation in cold climate versus usual care

Outcome: 6 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, left hand (% pred)

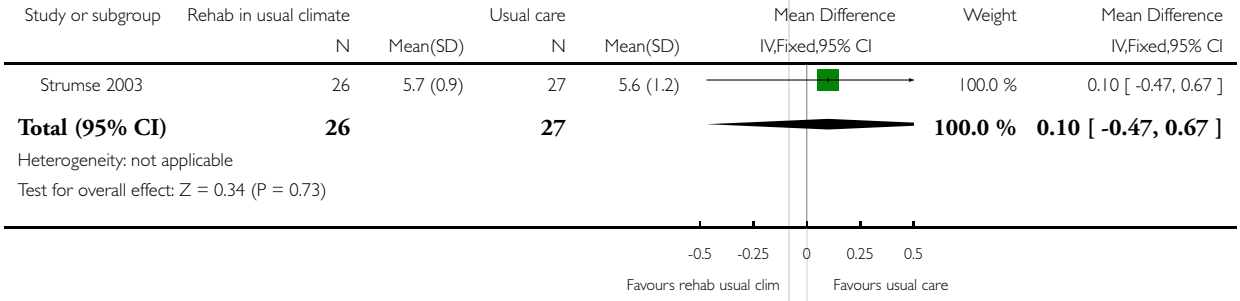


Analysis 8.7. Comparison 8 Rehabilitation in cold climate versus usual care, Outcome 7 Fatigue 3 months post-treatment - FSS (range 1 to 7).

Review: Treatment for postpolio syndrome

Comparison: 8 Rehabilitation in cold climate versus usual care

Outcome: 7 Fatigue 3 months post-treatment - FSS (range 1 to 7)

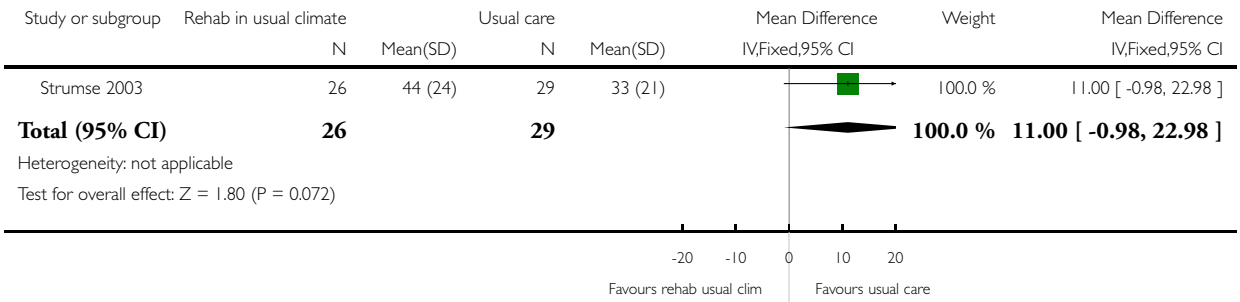


Analysis 8.8. Comparison 8 Rehabilitation in cold climate versus usual care, Outcome 8 Pain 3 months post-treatment - VAS (range 0 to 100 mm).

Review: Treatment for postpolio syndrome

Comparison: 8 Rehabilitation in cold climate versus usual care

Outcome: 8 Pain 3 months post-treatment - VAS (range 0 to 100 mm)

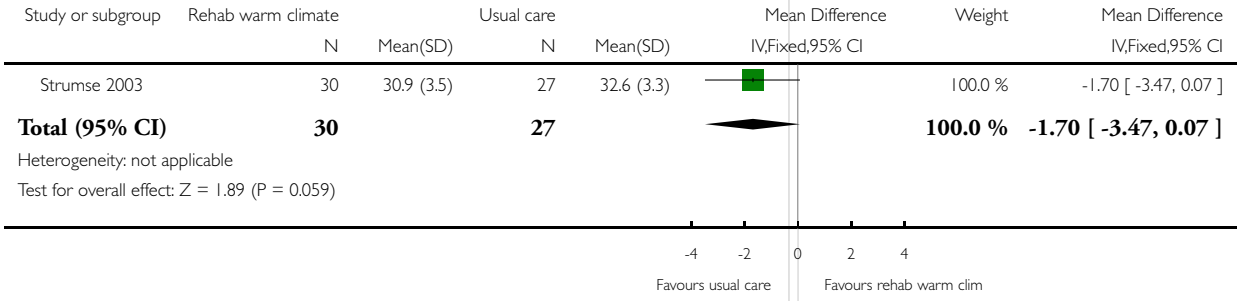


Analysis 9.1. Comparison 9 Rehabilitation in warm climate versus usual care, Outcome 1 Activity limitations 3 months post-treatment - Sunnaas ADL-index (range 0 to 36).

Review: Treatment for postpolio syndrome

Comparison: 9 Rehabilitation in warm climate versus usual care

Outcome: 1 Activity limitations 3 months post-treatment - Sunnaas ADL-index (range 0 to 36)



Analysis 9.2. Comparison 9 Rehabilitation in warm climate versus usual care, Outcome 2 Activity limitations 3 months post-treatment - Rivermead Mobility Index (range 0 to 15).

Review: Treatment for postpolio syndrome

Comparison: 9 Rehabilitation in warm climate versus usual care

Outcome: 2 Activity limitations 3 months post-treatment - Rivermead Mobility Index (range 0 to 15)

Study or subgroup	Rehab warm climate N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Strumse 2003	30	12.3 (2.8)	27	13.2 (2.5)		100.0 %	-0.90 [-2.28, 0.48]
Total (95% CI)	**30**		**27**			**100.0 %**	**-0.90 [-2.28, 0.48]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.28 (P = 0.20)

Analysis 9.3. Comparison 9 Rehabilitation in warm climate versus usual care, Outcome 3 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, right hand (% pred).

Review: Treatment for postpolio syndrome

Comparison: 9 Rehabilitation in warm climate versus usual care

Outcome: 3 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, right hand (% pred)

Study or subgroup	Rehab warm climate N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Strumse 2003	28	68 (30)	26	66 (34)		100.0 %	2.00 [-15.15, 19.15]
Total (95% CI)	**28**		**26**			**100.0 %**	**2.00 [-15.15, 19.15]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.23 (P = 0.82)

Analysis 9.4. Comparison 9 Rehabilitation in warm climate versus usual care, Outcome 4 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, left hand (% pred).

Review: Treatment for postpolio syndrome

Comparison: 9 Rehabilitation in warm climate versus usual care

Outcome: 4 Muscle strength 3 months post-treatment - Grippit Hand Grip Test, left hand (% pred)

Study or subgroup	Rehab warm climate N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Strumse 2003	28	62 (27)	27	56 (30)		100.0 %	6.00 [-9.10, 21.10]
Total (95% CI)	**28**		**27**			**100.0 %**	**6.00 [-9.10, 21.10]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.78 (P = 0.44)

Analysis 9.5. Comparison 9 Rehabilitation in warm climate versus usual care, Outcome 5 Fatigue 3 months post-treatment - FSS (range 1 to 7).

Review: Treatment for postpolio syndrome

Comparison: 9 Rehabilitation in warm climate versus usual care

Outcome: 5 Fatigue 3 months post-treatment - FSS (range 1 to 7)

Study or subgroup	Rehab warm climate N	Mean(SD)	Usual care N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Strumse 2003	30	5.2 (1.2)	27	5.6 (1.2)		100.0 %	-0.40 [-1.02, 0.22]
Total (95% CI)	**30**		**27**			**100.0 %**	**-0.40 [-1.02, 0.22]**

Heterogeneity: not applicable

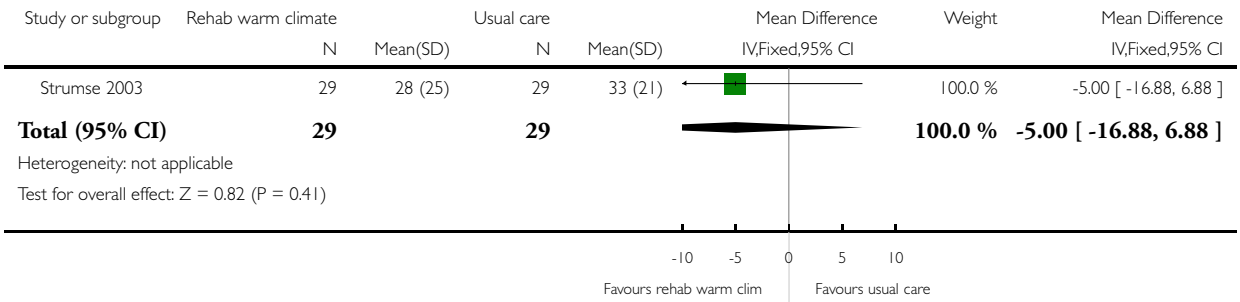
Test for overall effect: Z = 1.26 (P = 0.21)

Analysis 9.6. Comparison 9 Rehabilitation in warm climate versus usual care, Outcome 6 Pain 3 months post-treatment - VAS (range 0 to 100 mm).

Review: Treatment for postpolio syndrome

Comparison: 9 Rehabilitation in warm climate versus usual care

Outcome: 6 Pain 3 months post-treatment - VAS (range 0 to 100 mm)

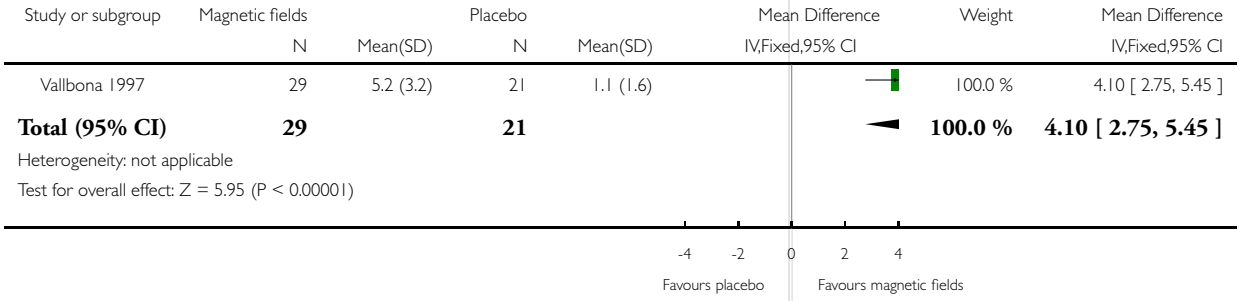


Analysis 10.1. Comparison 10 Static magnetic fields versus placebo, Outcome 1 Change in pain - intensity of pain felt on palpation of active trigger point (range 1 to 10).

Review: Treatment for postpolio syndrome

Comparison: 10 Static magnetic fields versus placebo

Outcome: 1 Change in pain - intensity of pain felt on palpation of active trigger point (range 1 to 10)



APPENDICES

Appendix 1. CENTRAL search strategy

1 Postpoliomyelitis Syndrome (MeSH)
2 post next polio*
3 (late NEAR/3 polio*) OR (late next effect* NEAR/3 polio*) OR (late next onset NEAR/3 polio*) OR (lateonset NEAR/3 polio*)
4 polio* NEAR/3 survivor*
5 prior next polio*
6 (#1 OR #2 OR #3 OR #4 OR #5)

Appendix 2. MEDLINE (OvidSP) search strategy

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized.ab.
4 placebo.ab.
5 drug therapy.fs.
6 randomly.ab.
7 trial.ab.
8 groups.ab.
9 or/1-8
10 exp animals/ not humans.sh.
11 9 not 10
12 Postpoliomyelitis Syndrome/
13 (post?polio* or post polio$).mp.
14 ((late adj3 polio$) or (late effect$ adj3 polio$) or (late?onset adj3 polio$) or (late onset adj3 polio$)).mp.
15 (polio$ adj3 survivor$).mp.
16 (prior?polio$ or prior polio$).mp.
17 or/12-16
18 11 and 17

Appendix 3. EMBASE (OvidSP) search strategy

1 crossover-procedure/
2 double-blind procedure/
3 randomized controlled trial/
4 single-blind procedure/
5 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw.
6 clinical trial/
7 or/1-6
8 animal/ not human/
9 7 not 8
10 Postpoliomyelitis Syndrome/
11 (post?polio* or post polio$).mp.
12 ((late adj3 polio$) or (late effect$ adj3 polio$) or (late?onset adj3 polio$) or (late onset adj3 polio$)).mp.
13 (polio$ adj3 survivor$).mp.
14 (prior?polio$ or prior polio$).mp.
15 or/10-14
16 9 and 15

Appendix 4. PsycINFO (OvidSP) search strategy

1 (post?polio* or post polio$).mp.
2 ((late adj3 polio$) or (late effect$ adj3 polio$) or (late?onset adj3 polio$) or (late onset adj3 polio$)).mp.
3 (polio$ adj3 survivor$).mp.
4 (prior?polio$ or prior polio$).mp.
5 poliomyelitis/ and syndromes/
6 or/1-5

Appendix 5. CINAHL (EBSCOhost) search strategy

S25 S18 and S24
S24 S19 or S20 or S21 or S22 or S23
S23 (prior polio*) or (prior?polio*)
S22 (polio* W3 survivor*)
S21 (late W3 polio*) or (late effect* W3 polio*) or (late onset W3 polio*)
S20 (post polio*) or (post?polio*) or (postpolio*)
S19 (MH "Postpoliomyelitis Syndrome") or (MH "Polio Survivors")
S18 S17 or S16 or S15 or S14 or S13 or S12 or S11 or S10 or S9 or S8 or S7 or S6 or S5 or S4 or S3 or S2 or S1
S17 TI random* or AB random*
S16 (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial or sham? or dummy))
S15 (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic)) and (TI (trial*) or AB (trial*))
S14 (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or systematic review*))
S13 (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind* or mask*))
S12 ABAB design*
S11 PT clinical trial or PT systematic review
S10 (MH "Factorial Design")
S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies")
S8 (MH "Meta Analysis")
S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison")
S6 (MH "Quasi-Experimental Studies")
S5 (MH "Placebos")
S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies")
S3 (MH "Clinical Trials+")
S2 (MH "Crossover Design")
S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample")

Appendix 6. Trials registers searches

poliomyelitis
postpolio syndrome

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 2, 2011

CONTRIBUTIONS OF AUTHORS

- Writing of protocol and review: FK, KU, NG, AB, MdV, FN
- Screening of titles and abstracts: FK, KU
- Assessment for inclusion: FK, KU
- Risk of bias assessment: FK, KU
- Disagreement resolution: NG
- Data extraction: FK, KU
- Data entry into RevMan: FK
- Data analysis: FK, KU
- Interpretation of results: FK, KU, NG, AB, MdV, FN

DECLARATIONS OF INTEREST

Three authors (AB, MdV, FN) carried out a randomised controlled trial on the effect of pyridostigmine in PPS (Horemans 2003). One author (NG) was involved in a randomised controlled trial on the effect of intravenous immunoglobulin in PPS (Farbu 2007). None of the authors have financial conflicts of interest in the findings of this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Prinses Beatrix Fonds (The Dutch Public Fund for Neuromuscular Disorders)/ ZonMw (The Netherlands Organisation for Health Research and Development), Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Methods: types of outcome measures:

- primary outcome measure 'change in activity limitations' narrowed to 'change in self-perceived activity limitations'

- added extra line: 'if a study did not report change from baseline scores, but final scores were available, these data were used for the analyses'

- deleted 'change in' (*outcome measure)*

2. Methods: assessment of risk of bias in included studies:

- further operationalisation of two risk of bias domains (blinding and incomplete outcome data)

3. Appendices:

- added extra line (line 6) in CENTRAL search strategy and PsychINFO search strategy

- new RCT filter for the MEDLINE search strategy

- new RCT filter for the EMBASE search strategy