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Corticosteroids or ACTH for acute exacerbations in multiple sclerosis (Review)

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[Intervention Review]

Corticosteroids or ACTH for acute exacerbations in multiple sclerosis

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ABSTRACT

Background

Corticosteroids are commonly used to improve the rate of recovery from acute exacerbation in multiple sclerosis (MS) patients. However, it is unclear just how effective these agents are and which is the best treatment schedule (type of drug, dose, frequency, duration of treatment and route of administration).

This review is un update of the Cochrane Review, "Corticosteroids or ACTH for acute exacerbations in multiple sclerosis," first published in *The Cochrane Library* 2000, Issue 4.

Objectives

Primary objectives were to determine the effects of corticosteroids and ACTH for the treatment of MS patients with acute exacerbation in terms of improvement of disability; reduction of risk of new exacerbations during follow-up; and prevention of disability progression at long-term follow-up. Secondary objectives included the frequency and severity of adverse effects and their acceptability in the light of benefits; the different effects of corticosteroids according to different doses and drugs, routes of administration, length of treatment and interval of time between onset of symptoms and randomisation, based on indirect comparisons; the different treatment effects according to disease course and the effect of corticosteroids or ACTH on magnetic resonance imaging as a surrogate marker of disease activity.

Search methods

The Trials Search Co-ordinator of the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group searched the Group's Specialised Register, which, among other sources, contains the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 2), MEDLINE, EMBASE, CINAHL, LILACS, PEDro and clinical trials registries (31 March 2013).

The review authors undertook handsearching and contacted trialists and pharmaceutical companies.

Selection criteria

All randomised, double-blind trials comparing corticosteroids or ACTH versus placebo in MS participants during acute exacerbations, regardless of age or severity, were evaluated.

Data collection and analysis

Two review authors selected trials for inclusion, assessed the risk of bias and extracted data independently. Disagreements were resolved by consensus among review authors. Study authors were contacted for additional information.

Main results

Six trials, published between 1961 and 1998, contributed to this review. The current update did not identify new trials. A total of 377 participants (199 treatment, 178 placebo) were randomly assigned. The drugs analysed were methylprednisolone (MP) (four trials, 140 participants) and ACTH (two trials, 237 participants). Overall, administration of MP or ACTH favoured recovery from acute exacerbation in MS participants: use of either agent decreased by more than 60% the probability of the condition getting worse or stable within the first five weeks of treatment (odds ratio (OR) 0.37, 95% confidence interval (95% CI) 0.24 to 0.57; reduced disability of 1.5 points in the Kurtzke Expanded Disability Status Scale (EDSS) score at the first week of therapy, mean difference -1.47, 95% CI -2.25 to -0.69). The overall quality of evidence according to GRADE levels was moderate. Evidence was insufficient to show whether steroids or ACTH treatment prevented new exacerbations and worsening of long-term disability. Indirect comparisons suggest a significantly greater effect of MP versus ACTH, with MP conferring greater benefit compared with ACTH (OR 0.20, 95% CI 0.09 to 0.45 vs OR 0.46, 95% CI 0.28 to 0.77), and with intravenous MP proving more effective than oral MP (OR 0.12, 95% CI 0.04 to 0.42 vs OR 0.29, 95% CI 0.10 to 0.89) in decreasing the risk of getting worse or stable within the first five weeks of treatment. The time interval from onset of exacerbation to start of treatment administration does not seem to influence the outcome. Short-term (five days) courses of intravenous MP seem to be more effective than long-term treatment (15 days) (OR 0.13, 95% CI 0.02 to 0.75 vs OR 0.22, 95% CI 0.09 to 0.57). No data are available beyond one year of follow-up to allow evaluation of any effect on long-term progression. One study reported that short-term treatment with intravenous high-dose MP was not associated with adverse events. However, gastrointestinal symptoms and affective disorders were significantly more common in the oral high-dose MP group than in the placebo group. Weight gain and edema were significantly more frequent in the ACTH group than among controls.

Authors' conclusions

We found evidence that corticosteroids, notably MP, are effective in the treatment of acute exacerbation, increasing the probability of ameliorating the episode and speeding up patient recovery. Data were insufficient to permit reliable estimation of the effects of corticosteroids on prevention of new exacerbations and long-term disability.

PLAIN LANGUAGE SUMMARY

The use of anti-inflammatory corticosteroids for treating acute worsening in people with multiple sclerosis

This review is un update of the Cochrane Review, "Corticosteroids or ACTH for acute exacerbations in multiple sclerosis," first published in *The Cochrane Library* 2000, Issue 4.

Multiple sclerosis (MS) is a chronic disease of the nervous system. Focal inflammation impairs the ability of white matter tracts to conduct electrical impulses and produces acute episodes of neurological dysfunction called *relapses*. During a relapse of the disease, the symptoms may cause different levels of impairment with variable recovery. Relapse-related sequelae may accumulate during the course of the disease and cause permanent disability. Disability is commonly evaluated according to the Kurtzke scale, which is scored over a range of 10 points (0 = no disability, 10 = death).

Corticosteroids reduce the inflammation in the brain and the spinal cord and are the first drugs of choice to treat exacerbations of MS. The objective of this review was to determine the efficacy of corticosteroids or adrenocorticotrophic hormone (ACTH) versus no treatment (placebo) in decreasing disability in MS patients affected by acute relapse. Prevention of long-term morbidity was also evaluated. Secondary objectives were to assess the safety and efficacy of different types of drugs and different schedules of treatment.

Six studies published between 1961 and 1998 have been included, with a total of 377 participants.

The main results of this review show that corticosteroids (methylprednisolone (MP)) or ACTH favoured recovery from acute exacerbation, increasing by more than 60% the probability of ameliorating the episode within the first five weeks of treatment. Clinical recovery was found to be accelerated and reduction of disability was assessed as a 1.5-point change in EDSS score during the first week of therapy. The quality of evidence was moderate. The drugs were well tolerated.

No clear data on long-term effects were found.

Evidence on the efficacy of different types or schedules of therapies was limited. Indirect comparisons suggest a significantly greater effect of MP versus ACTH. A short-term course (5 days) of MP seems to be more effective than long-term treatment (15 days). The interval between exacerbation onset and the start of treatment does not seem to influence the outcome.

Overall, this review provides evidence to support the use of corticosteroids in treating relapses in people with MS. These agents are effective over the short term in improving symptoms, thus favouring recovery.

Summary of findings for the main comparison. Corticosteroids or ACTH versus placebo for acute exacerbations in multiple sclerosis

Corticosteroids or ACTH versus placebo for acute exacerbations in multiple sclerosis

Patient or population: multiple sclerosis patients with acute exacerbations
Settings: hospital setting
Intervention: corticosteroids or ACTH 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	Corticosteroids or ACTH versus placebo				
Worse or unimproved within 5 weeks from randomisation Follow-up: 5 weeks	**Study population**		**OR 0.37** (0.24 to 0.57)	330 (5 studies)	⊕⊕⊕⊖ **moderate**	
	61 per 100	**36 per 100** (27 to 47)				
	Medium-risk population					
	75 per 100	**53 per 100** (42 to 63)				
Mean disability (EDSS) score—at 1 week after randomisation Follow-up: 1 week		Treated participants' EDSS was **1.47 lower** (2.25 to 0.69 lower) than placebo	Mean difference	62 (2 studies)	⊕⊕⊕⊖ **moderate** [1]	
Participants with new exacerbations during follow-up—at 6 months Follow-up: 6 months	**Study population**		**OR 1.72** (0.57 to 5.19)	51 (1 study)	⊕⊖⊖⊖ **very low** [2,3]	
	52 per 100	**65 per 100** (38 to 85)				
	Medium-risk population					
	52 per 100	**65 per 100** (38 to 85)				

*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; **OR:** Odds ratio.

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

[1] The confidence interval was wild (-2.25 to -0.69).
[2] Sellebjerg's study was judged at low quality for high-risk performance and detection.
[3]Only one study of low quality (Sellebjerg) described this outcome.

BACKGROUND

This review is un update of the Cochrane Review, "Corticosteroids or ACTH for acute exacerbations in multiple sclerosis," first published in *The Cochrane Library* 2000, Issue 4.

Description of the condition

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) whose aetiology and pathogenesis are still to be clarified. Both genetic and environmental factors seem to determine susceptibility to the disease (Compston 1999; Willer 2000).

MS is a relatively rare disease (incidence of 2 to 10 cases per 100,000 persons per year; in Europe, Canada and the United States, prevalence rates range between 60 and more than 100 cases per 100,000 inhabitants) (Pugliatti 2002 ; WHO 2008) that affects young adults with nearly normal life expectancy. Consequently, it is one of the most common causes of disability in young adults. The most characteristic clinical feature is the occurrence of exacerbations, which can be defined as a clinical syndrome of acute or subacute onset, in the absence of fever or infection, that can last from days to months. Disability may occur if recovery from an exacerbation is not completed. When the clinical course between two exacerbations is stable, the patient is in the relapsing-remitting (RR) phase of the disease. In general, exacerbations are more frequent early in the course of the disease, and progressive worsening is more common in later stages (secondary progressive course (SP)) either with or without the occurrence of superimposed exacerbations. In a small proportion of patients, the disease is progressive from onset without (primary progressive (PP)) or with superimposed exacerbations (progressive relapsing (PR)) (Lublin 1996).

During the initial stage of the inflammatory phase, lymphocytes with encephalitogenic potential are activated in the periphery by different factors not well clarified. These phenomena produce a breach in the blood-brain barrier (BBB), leading to infiltration of immune cells into the CNS and focal demyelination (Schweingruber 2011). During an acute relapse, levels of pro-inflammatory mediators and trophic factors such as tumour necrosis factor-alpha (TNFα) and inducible nitric oxide synthase (iNOS) are increased, leading to tissue injury (Lindquist 2011).

BBB disruption is an early marker of a recent lesion of MS and can be demonstrated by means of gadolinium-DTPA (Gd-DTPA) with magnetic resonance imaging (MRI). Clinical findings in patients with MS are correlated with the detection of contrast-enhancing acute plaques through MRI techniques (Atalay 2005).

Description of the intervention

ACTH is secreted from the anterior pituitary and stimulates the adrenal cortex. More specifically, it stimulates secretion of glucocorticoids such as cortisol, and it has little control over secretion of aldosterone, the other major steroid hormone from the adrenal cortex. Therapeutic use of ACTH has been proposed for infantile spasm, nephrotic syndrome and acute exacerbations of MS (Levine 2012).

Synthetic compounds, which have greater anti-inflammatory effects than ACTH and less effect on salt and water balance, are usually preferred for the treatment of inflammatory disorders. These compounds include dexamethasone, which is almost exclusively glucocorticoid in its actions, as well as prednisone, prednisolone, betamethasone, triamcinolone and methylprednisolone. Glucocorticoids are formulated in various types, including oral and injectable dosage forms.

Glucocorticoid medications have multiple mechanisms of action when used to treat demyelinating diseases. Most of the cellular and physiological effects of glucocorticoids occur via the glucocorticoid receptor (one member of a nuclear receptor superfamily). They impact gene transcription through several different mechanisms and are potentially involved in the modulation of neuro-inflammation, including induction of apoptosis, repression of pro-inflammatory mediators and expansion of suppressor cells. Corticosteroids reduce the inflammatory response by inducing several effects on the immune system. They inhibit lymphocyte proliferation and cell-mediated immune response; decrease circulating T helper cells, eosinophils and monocytes; down-regulate cytokine gene expression; suppress synthesis of pro-inflammatory mediators, including interferon-γ and TNFα; and inhibit the expression of class II histocompatibility antigens on the macrophage surface (Schweingruber 2011).

Moreover, these drugs have independent effects on BBB permeability and on neural tissue (McEwen 1997; Sapolsky 2000).

How the intervention might work

Therapeutic strategies have been directed at treating the exacerbation, preventing new exacerbations and avoiding progression of disability. Treatment of exacerbations since the 1950s has been based on the use of ACTH and corticosteroids (Glaser 1951).

Glucocorticoid treatments are commonly used in clinical practice because different studies have demonstrated their efficacy in improving the speed of functional recovery of participants with acute MS relapses (Tremlett 1998) and in inducing clinical improvement in RR MS participants. This effect seems to be correlated with reduced inflammation and myelin breakdown, indicating that the action of glucocorticoids is accompanied by improved BBB integrity (Barkhof 1992). The effect of corticosteroids in suppressing Gd-enhanced MRI disease activity has been confirmed: MP is effective in reducing Gd-enhancing lesions in MS patients soon after an acute relapse (Martinelli 2009).

The probability of improvement after MP treatment in optic neuritis (ON) or in attacks of MS seems to be higher among patients with enhancing lesions on baseline MRI. MP treatment suppressed Gd enhancement after one week ($P < 0.001$) and three weeks ($P = 0.001$), showing that resolution of intrathecal inflammation is a major effect of methylprednisolone (Sellebjerg 2003).

Clinical improvement of MS patients with relapse following treatment with MP may be associated with an immediate, but not long-term, modification of serum levels of chemokine (C-C motif) ligand 2 (CCL2) and Interleukin 12 (IL-12) (Rentzos 2008).

These results support the use of MP treatment for MS relapses; MP induces immediate post-treatment and short-term effects on the immune system, along with clinical and radiological improvement. However, the long-term influence of MP treatment on the course of the disease remains uncertain (Martínez-Cáceres 2002).

The results of trials that analysed direct comparisons have shown no significant differences between ACTH and MP in both rate and degree of recovery after exacerbation (Thompson 1989). Uncertainty is ongoing regarding the best type and regimen of corticosteroids for the treatment of patients with MS (Repovic 2011).

Why it is important to do this review

Several narrative reviews have been published on the use of corticosteroids or ACTH in MS, but the results of all randomised controlled trials (RCTs) evaluating their effects versus placebo had never been systematically reviewed.

Uncertainty continues regarding the type, the dosage and the best regimen of corticosteroids for the treatment of patients with MS. Furthermore, no conclusive information is available on optimal timing of the start of treatment in relation to relapse onset and on how long the therapeutic effect may persist.

Different treatment regimens are prescribed in clinical practice (Morrow 2009) because no convincing evidence suggests that clinical benefit is influenced by the route of administration or the dosage of glucocorticoid, or by the type of glucocorticoid prescribed.

The results of trials using direct comparisons have shown no significant differences between ACTH and MP in terms of rate and degree of recovery after exacerbation (Thompson 1989). However, other studies have shown that MP leads to faster recovery than ACTH, and that high doses of MP are more effective than lower doses in both clinical and MRI outcomes (Repovic 2011), A previous study (Barnes 1997) and a systematic review (SR) (Burton 2012) comparing intravenous versus oral steroid therapy for MS relapses did not demonstrate any significant differences in clinical (benefits and adverse events), radiological or pharmacological outcomes.

A recent SR (Gal 2012) conducted to evaluate the efficacy of steroids in optic neuritis (ON) reported that no conclusive evidence suggests benefit in terms of return to normal visual acuity, visual field or contrast sensitivity with intravenous or oral corticosteroids versus placebo in acute ON at six and 12 months of follow-up.

An SR based on three trials (Ciccone 2008), all classified as having high risk of bias, concluded that evidence is insufficient to show that long-term corticosteroid treatment delays progression of long-term disability in MS patients: Only one study showed that administration of pulsed high-dose intravenous MP is associated with a significant reduction in the risk of long-term disability progression in patients with RR MS. The authors suggested the need for further adequately powered, high-quality RCTs.

This review is un update of the Cochrane Review, "Corticosteroids or ACTH for acute exacerbations in multiple sclerosis," first published in *The Cochrane Library* 2000, Issue 4.

OBJECTIVES

Primary objectives were to determine the effects of corticosteroids and ACTH for the treatment of MS participants with acute exacerbation in terms of:

1. improvement of disability;
2. reduction of risk of new exacerbations during follow-up; and
3. prevention of disability progression at long-term follow-up.

Secondary objectives were:

1. the frequency and severity of adverse effects and their acceptability in the light of benefits;
2. the different effects of corticosteroids according to different doses and drugs, routes of administration, length of treatment and interval of time between onset of symptoms and randomisation, based on indirect comparisons;
3. the different treatment effects according to disease course (first attack, RR, SP and PR participants); and
4. the effect of corticosteroids or ACTH on MRI as a surrogate marker of disease activity.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised double-blind controlled trials (RCTs) of corticosteroids or ACTH versus placebo in acute relapse of MS were included. Both non-controlled and non-randomised trials were excluded. Trials comparing add-on active treatments in all arms were excluded.

Types of participants

MS patients treated for acute exacerbation irrespective of their disease course (RR, SP, PR) categorised according to the classification of Lublin and Reingold (Lublin 1996) were included. Patients with definitive diagnosis of MS according to Poser's (Poser 1983) or Mc Donald's criteria (McDonald 1977) were included. A relapse was defined as an episode typical of an acute inflammatory demyelinating event in the CNS, with or without objective confirmation, with duration of at least 24 hours, in the absence of fever or infection. However, any relapse definition provided by the authors was accepted.

Types of interventions

Any type of corticosteroid—methylprednisolone (MP), prednisone, prednisolone and dexamethasone—or ACTH versus placebo was evaluated independent of dosage, route of administration, interval of time between onset of symptoms and randomisation and duration of treatment.

Types of outcome measures

The following outcome measures were evaluated according to three main clinical domains.

Treatment of acute exacerbation

1. Number of MS participants in the allocated treatment groups worse off or with no improvement during the acute phase, within a period no longer than 12 weeks from randomisation. Worsening of disability was defined as an increase of at least one point on the entry Kurtzke Expanded Disability Status Scale (EDSS) or equivalent score. EDSS is widely used as an ordinal rating scale ranging from 0 to 10, with high scores reflecting increasing severity of the disability (Kurtzke 1983).
2. Mean disability score and standard deviation (SD) in the allocated treatment groups at 1, 4, 8 and 12 weeks.
3. Time to start of improvement in days.

Prevention of new exacerbations

1. Number of participants with at least one exacerbation at six months, one year, two years and three years from randomisation.
2. Exacerbation-free time.

Worse or no improvement at long-term follow-up

1. Number of participants in the allocated treatment groups worse off or with no improvement from 12 weeks after the acute exacerbation until the end of the trial follow-up.
2. Mean disability score and SD in the allocated treatment groups from 12 weeks after the acute exacerbation until the end of the trial follow-up period.

Search methods for identification of studies

Electronic searches

The Trials Search Co-ordinator searched the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group Trials Register (31 March 2013), which is updated regularly and contains trials identified from the following.

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 2).
2. MEDLINE (PubMed) (1966 to 31 March 2013).
3. EMBASE (Embase.com) (1974 to 31 March 2013).
4. CINAHL (Ebsco host) (1981 to 31 March 2013).
5. LILACS (Bireme) (1982 to 31 March 2013).
6. PEDro (1990 to 31 March 2013).
7. Clinical trials registries (http://clinicaltrials.gov).

Information on the Group's Trials Register and details of search strategies used to identify trials can be found in the 'Specialised Register' section within the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group's module.

The keywords used to search for this review are listed in Appendix 1

Searching other resources

1. Bibliographic references of identified studies were searched for references to additional studies.
2. Handsearching was done to identify recent (1997 to 2013) retrieved articles and the abstracts of neurological and multiple sclerosis congresses and symposia, conference proceedings, dissertations and other forms of reports for which trials relevant to the review are likely to have been published (1997 to 2013).
3. Personal contact was made with corresponding authors/researchers of relevant trials or with review authors.
4. Contact was made with Pharmacia & Upjohn and with Bruno Farmaceutici in an effort to identify any unpublished trials.

Data collection and analysis

Selection of studies

For the update of the review, two review authors (AC,LLM) screened independently titles and abstracts of the citations retrieved by the literature search to determine their inclusion/exclusion in the review. Disagreements were resolved by discussion among the two review authors.

Data extraction and management

Two review authors (FB, GF) independently extracted data from the selected trials using standardised forms. A third review author (AC) cross-checked the data, and disagreements were resolved through consensus. We sought data on the number of participants with each outcome event, by allocated treatment group, irrespective of compliance, and whether or not the patient subsequently was deemed ineligible or otherwise was excluded from treatment or follow-up, to allow an "intention-to-treat" analysis. We extracted the numbers of worse or unimproved participants and of participants with new exacerbations during follow-up by allocated treatment groups. We also extracted the mean and SD of EDSS in treatment and placebo groups during follow-up. If available, we extracted data on the delay from exacerbation onset to trial entry, the type of steroid regimen used, the presence of confounders and the type and severity of adverse reactions. We also sought data on MRI results reported in the allocated treatment groups at different follow-up times.

Review authors recorded details of the randomisation method, baseline participant characteristics, blinding, whether an intention-to-treat analysis was done, the number of participants withdrawn from the trial after randomisation and the number with incomplete follow-up.

Assessment of risk of bias in included studies

The methodological criteria were based on the *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.1.0 (Higgins 2011). Two review authors (AC,LLM) independently evaluated the methodological quality of the studies using the 'Risk of bias' tool under the domains of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome and other biases. Disagreements among the review authors on the methodological quality of the identified studies were discussed and resolved by consensus.

Attrition bias was judged "high" if the proportion of lost at follow up participants lost to follow-up was greater than 20%.

We considered studies to be of high methodological quality if the risk of bias for selection, detection and attrition bias was low . We rated studies as having low methodological quality if one of these domains was judged at high risk of bias and medium if was deemed medium in all other cases.

Measures of treatment effect

For each binary outcome, we calculated a weighted estimate of the odds ratio (i.e. the ratio of the odds of an unfavourable outcome among treatment-allocated participants to the corresponding odds among controls) along with the relative 95% confidence interval across studies using the Peto fixed-effect method. When indicated, we calculated absolute outcome events (i.e. the number of events avoided for every 1000 participants treated) using risk reduction statistics. For disability score, we estimated the mean difference of overall weight across trials (Review Manager 2012).

Unit of analysis issues

We performed separate analyses for the main outcome measures while mantaining the original allocation groups.

Dealing with missing data

Because data were available from published reports, trial authors have not been contacted.

Assessment of heterogeneity

We tested heterogeneity among trial results using a standard Chi^2 test.

Assessment of reporting biases

Fewer than ten studies could be included in the meta-analysis. Therefore funnel plots could not be constructed to indicate possible publication bias.

Data synthesis

We performed meta-analysis using a fixed-effect model. A random-effects model was used if heterogeneity was found ($I^2 > 50\%$).

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses according to the drug (MP, ACTH), the length of treatment (i.e. less than or equal to five days, greater than five days), the route of administration (oral, intravenous), the interval time from exacerbation onset to randomisation (i.e. less than or equal to two weeks, greater than two weeks) and the type of disease course at randomisation (RR, SP or PR). It should be noted that these comparisons are indirect rather than direct randomised comparisons.

Sensitivity analysis

We did not perform a sensitivity analysis because of the low number of included trials and the lack of heterogeneity. However, a worst-case scenario was evaluated for assessment of results of primary outcomes.

RESULTS

Description of studies

Results of the search

We identified 221 records, 211 from database searching and ten from other sources. One hundred and seventy six were excluded due to lack of pertinence. Forty five full texts were assessed for eligibility, 39 were excluded and six included in the review (Figure 1)

Figure 1. Study flow diagram.

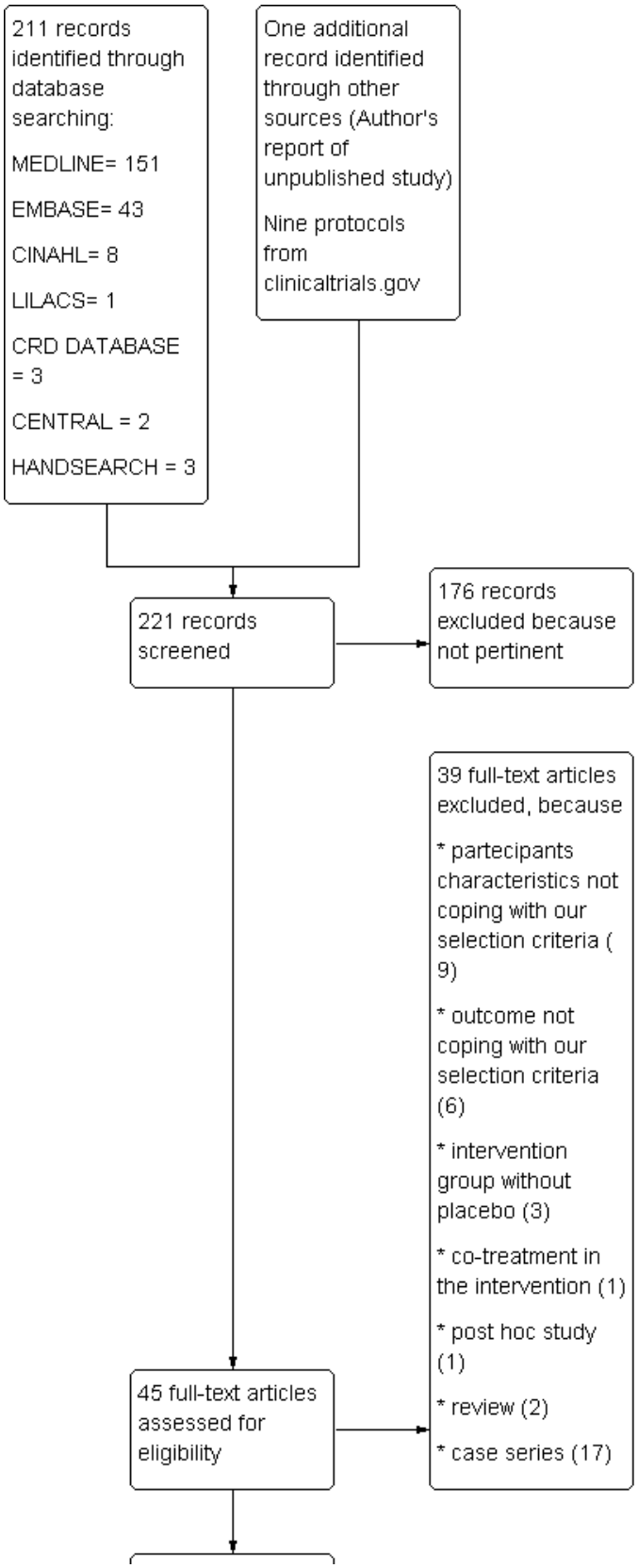
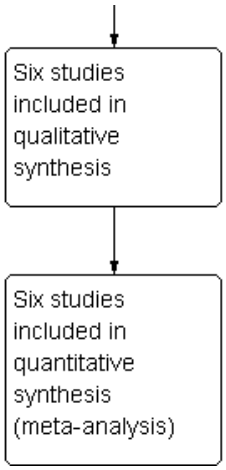


Figure 1. (Continued)



As compared with the first version we have retrieved 132 new records, but all of them were excluded and the final analysis was unchanged.

Included studies

In total, six trials contributed to this review: The earliest was published in 1961 and the most recent in 1998 (Miller 1961a; Rose 1970; Durelli 1986; Milligan 1987; Filipovic 1997; Sellebjerg 1998); a total of 377 participants (199 treatment, 178 placebo) were randomly assigned. One multi-centre RCT of intramuscular ACTH (Rose 1970) accounted for 197 (52%) of the total 377 experimental participants (Characteristics of included studies).

Two studies (Durelli 1986; Sellebjerg 1998) included only RR participants in acute exacerbation. Four trials (Miller 1961a; Rose 1970; Milligan 1987; Filipovic 1997) included both RR and PR participants in exacerbation. The trial of Milligan 1987 included both participants in acute exacerbation and participants out of exacerbation; only participants in acute exacerbation were included in our review. Participants were randomly assigned within two weeks (Miller 1961a), four weeks (Sellebjerg 1998) or eight weeks (Durelli 1986; Rose 1970; Milligan 1987) following onset of exacerbation. Data on randomisation time were not available from one study (Filipovic 1997). The agents that were compared with placebo included the following.

1. Methylprednisolone (MP) 500 mg daily administered perorally for five days followed by a tapering of dose for 10 further days (Sellebjerg 1998); 1000 mg daily administered intravenously for five days (Filipovic 1997); 500 mg daily administered intravenously for five days (Milligan 1987); 15 mg/kg daily administered intravenously for three days followed by an orally administered tapering for 12 days further (Durelli 1986).
2. ACTH 40 UI per dose twice daily administered intramuscularly for seven days, 20 UI per dose twice daily for four days and 20 UI per dose daily for three days (Rose 1970); ACTH 60 UI per dose twice daily for seven days, 40 UI per dose twice daily for seven days and 60 UI, 40 UI and 20 UI per dose on the second, fourth and sixth days of the third week (Miller 1961a)

Exclusion criteria were specified in four trials (Rose 1970; Milligan 1987; Filipovic 1997; Sellebjerg 1998) (Characteristics of included studies).Three trials (Durelli 1986; Filipovic 1997; Sellebjerg 1998) used clinical and paraclinical diagnostic criteria (Poser 1983), one study (Milligan 1987) used clinical diagnostic criteria only (McDonald 1977) and one study (Rose 1970) used diagnostic criteria defined in its own study protocol. In one trial (Miller 1961a), diagnostic criteria were not formally defined. The scheduled follow-up period varied from seven days (Filipovic 1997) to one year (Sellebjerg 1998).

Five trials (Miller 1961a; Rose 1970; Durelli 1986; Milligan 1987; Sellebjerg 1998) evaluated the numbers of participants who improved during treatment and during the follow-up period without treatment. Comparable definitions of improvement were used in the trials and included the following.

1. An improvement of one or more points in Kurtzke EDSS score (Durelli 1986; Milligan 1987; Sellebjerg 1998) or in Kurtzke Disability Status Scale (DSS) score (Rose 1970).
2. Improvement or worsening judged by one examiner who was unaware of the group to which the participant belonged (Miller 1961a).

One trial (Filipovic 1997) reported mean and SD of EDSS scores before and after completion of therapy for both groups.
One trial (Durelli 1986) recorded information on the time from the start of treatment to the start of improvement.
One trial (Sellebjerg 1998) provided information on recurrent exacerbations at six months and one year and on disability progression at one year. Measures of MRI were reported in a post hoc study (Sellebjerg 2003). The study was performed in a subgroup of participants who had ON or who had had attacks of MS and had participated in two randomised, placebo-controlled treatment trials (Sellebjerg 1998; Sellebjerg 1999b). Only the first RCT (Sellebjerg 1998) was included in this review. The presence of gadolinium-enhancing lesions at the start of treatment was correlated with clinical response, showing that the presence of gadolinium-enhancing lesions at baseline increased the probability of improving. The data were not analysed because the details of individual participants were combined.

BASELINE PARTICIPANT CHARACTERISTICS

Equivalence between treatment and control groups in terms of baseline participant characteristics was noted in the large trial of Rose (Rose 1970) and in four smaller trials (Miller 1961a; Durelli

1986; Filipovic 1997; Sellebjerg 1998). In one small trial (Milligan 1987), treated participants had higher disability scores at entry than controls, but this difference should not bias the overall results because evidence did not indicate that more severely affected participants achieve greater spontaneous recovery than individuals with milder relapse.

Excluded studies

We excluded thirty-nine studies after reading the full published papers: Seven studies were RCTs of corticosteroids or ACTH in MS participants who were not in acute exacerbation (Miller 1961b; Martin 1964; Tourtellotte 1965; Boman 1966; Millar 1967; Kiessling 1987; Gunal 1996); four studies were dose comparison trials without a placebo group (Goodkin 1998; Zivadinov 2001; Visser 2004; Dong 2012); one study was an open RCT of the long-term effects of ACTH treatment for acute relapse; in this study, outcome results were unclear (Hoogstraten 1990). In one RCT of methylprednisolone, only instrumental, not clinical, outcomes were reported (Compston 1987); from one double-blind RCT that included both progressive and relapsing-remitting MS participants during acute exacerbations, we were unable to extract outcome data (Rinne 1968); in one RCT of oral high-dose methylprednisolone, participants with acute optic neuritis were treated (Sellebjerg 1999b); one RCT was confounded because the treatment groups received another co-treatment and only neuroendocrine effects were studied (Then Bergh 2001). One study examined the MRI effects of steroid treatment on all MS participants in an RCT of oral interferon beta (Hoogervorst 2002). One study was a double-blind controlled clinical trial (CCT) of ACTH treatment, and the author was unable to provide outcome data (Marforio 1984). Eleven studies were case series (Merritt 1954; Dowling 1980; Buckley 1982; Newman 1982; Kesselring 1989; Rumbach 1990; Barkhof 1991; Burnham 1991; Miller 1992; Frequin 1994; Beretta 1997); six studies were case series, and the authors did not report clinical parameters (Tourtellotte 1980; Trotter 1980; Frequin 1993; Whitaker 1993; Versino 1994; Martinez-Caceres 2002). Advertisement for trials among colleagues identified an unpublished RCT for which a draft was obtained. However, this study was not included because participants were not in an acute phase of disease (Ciccone 1998). Three studies were narrative reviews (Kupersmith 1994; Repovic 2004; Schweingruber 2011) (Characteristics of excluded studies).

Risk of bias in included studies

The data are reported in the tables of included studies (Characteristics of included studies) and in the figures (Figure 2; Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

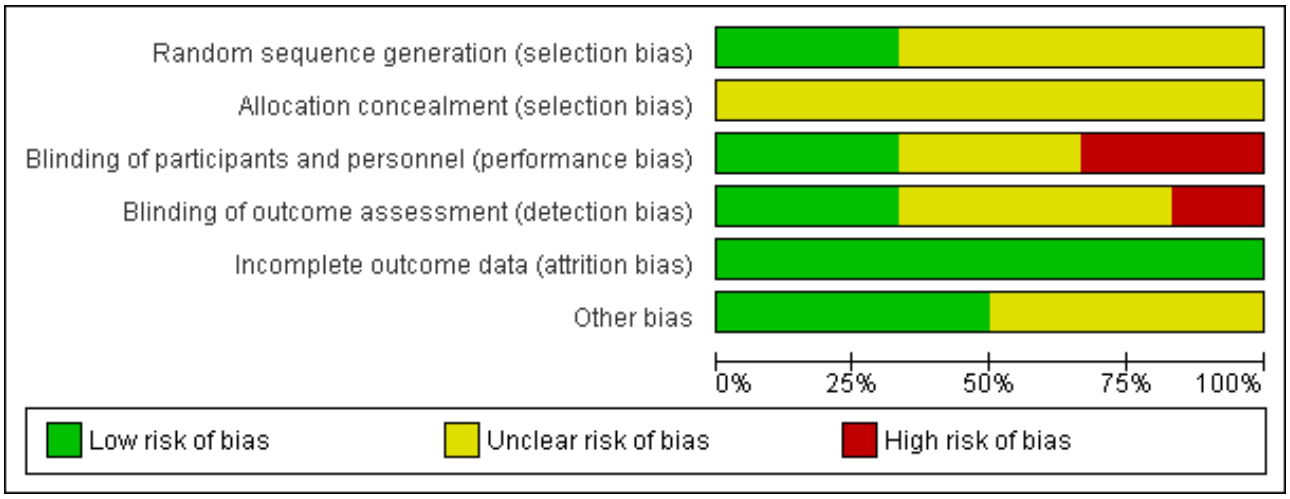
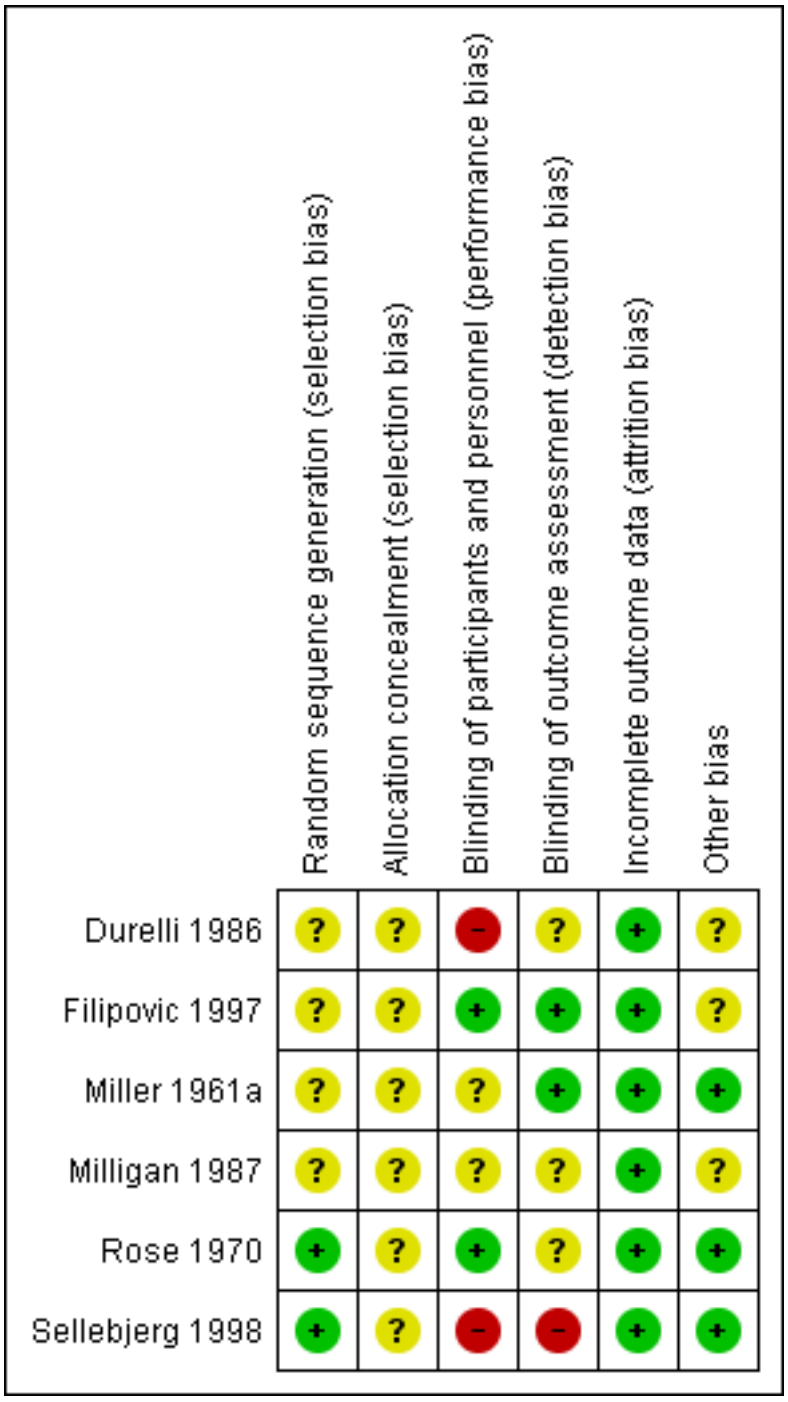


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



No studies were classified as of good quality (no low risk of bias for selection, detection and attrition bias). One study (Sellebjerg 1998) was judged to have low quality because of high risk of bias in at least one domain (detection). The other studies were considered to be of medium quality.

RANDOMISATION

The method of randomisation was adequate in two trials (Rose 1970; Sellebjerg 1998).

Details of the method of randomisation were not provided in four trials (Miller 1961a; Durelli 1986; Milligan 1987; Filipovic 1997).

Allocation

No paper describes the allocation concealment. This argument was underlined only later in the literature.

Blinding

All trials were declared to be double-blind. Performance bias was at high risk for two RCTS (Durelli 1986; Sellebjerg 1998) because of the occurrence of side effects in the treated group, at unclear risk for two (Miller 1961a; Milligan 1987) and at low risk for the other two studies (Rose 1970; Filipovic 1997).

In the multi-centre study (Rose 1970), each participating centre was supplied with numbered sets of indistinguishable ampules from a Central Office; no substitution from one set of ampules to the other was allowed.

Detection bias was at high risk for only one trial (Sellebjerg 1998), unclear for three (Rose 1970; Durelli 1986; Milligan 1987) and low for the other two. An analysis of the degree of blindness achieved in one study (Rose 1970) showed that at the 28th day of follow-up, the physicians correctly thought that 58% of the participants had received treatment and 80% had received placebo. Most of the participants who showed side effects attributable to the medication were found in the "ACTH-yes" group, adding notably to the "correct " scores for treated participants and providing nearly half of the "incorrect" scores among the placebo participants. In the trial of Filipovic (Filipovic 1997), the neurological examinations were performed by independent neurologists, blinded to treatment, and results were collected at the end of the study. In the Miller study (Miller 1961a), the subjective outcome was evaluated by one unaware observer.

Incomplete outcome data

Only one study (Durelli 1986) was judged to be at high risk. Durelli describes 13 participants in the treatment group but refers to results for 12 or 11 in the outcomes tables without justifying these discrepancies.The other studies were considered to be at low risk for this domain (Characteristics of included studies).

Selective reporting

No evidence of selective reporting was noted.

Other potential sources of bias

An intention-to-treat analysis was possible in three trials, which contributed about 76% of the data (Miller 1961a; Rose 1970; Sellebjerg 1998). In the remaining three trials (Durelli 1986; Milligan 1987; Filipovic 1997), a total of seven participants (1.8% overall) were excluded after randomisation. No information on outcome events was available for these participants.

All studies used EDSS or DSS scores to measure outcome of treatment, except Miller (Miller 1961a), who performed a subjective evaluation of improvement, classified in three categories but corresponding to the outcome measures selected for this review.

Only two studies declared a grant: The Rose 1970 trial was supported by the National Institute of Neurological Diseases and Blindness and the National Multiple Sclerosis Society, and Sellebjerg 1998 was supported by the Danish Multiple Sclerosis Society, the Johnsen Memorial Foundation and Pharmacia & Upjohn.

Effects of interventions

See: **Summary of findings for the main comparison** Corticosteroids or ACTH versus placebo for acute exacerbations in multiple sclerosis

TREATMENT OF ACUTE EXACERBATION

1. Participants worsened or unimproved within five weeks from randomisation.

Data from five trials (Miller 1961a; Rose 1970; Durelli 1986; Milligan 1987; Sellebjerg 1998) with 330 participants (87% of participants included in the review) were available on this outcome. ACTH or MP therapy was associated with a significant reduction in the risk of worsening or no improvement within five weeks (Peto odds ratio (OR) 0.37, 95% confidence interval (95% CI) 0.24 to 0.57). In absolute terms, this means that 257 more participants improved for every 1000 participants treated with corticosteroids or ACTH (95% CI 144 to 349 improved). No statistically significant heterogeneity for this outcome was noted among the studies.

A prespecified sensitivity analysis showed no statistically significant difference in the effects of treatment on the likelihood of worsening or not improving at final follow-up when participants, who were randomly assigned to treatment and then excluded, were considered as worst outcome events (number of events in treated participants = 65/177; number of events in controls = 94/156; OR 0.39, 95% CI 0.25 to 0.60).

2. Mean disability score at one week and at four weeks from randomisation.

Two trials (Milligan 1987; Filipovic 1997) including 62 participants (16% of participants included in the review) reported disability score at one week from randomisation. Weighted mean differences and 95% CI for EDSS score were -1.47 (95% CI -2.25 to -0.69).
Only one study (Milligan 1987) reported this outcome at four weeks from randomisation: No significant difference was noted between participants treated with intravenous MP and controls.

3. Time to start of improvement.

One study (Durelli 1986) including 21 participants (only 6% of participants included in the review) reported data on this outcome. The time to improvement was shorter (mean 32 days, SD 9 days) in the intravenous MP group than in the control group (mean 45 days, SD 9 days). This result was statistically significant ($Chi^2 = 3.29$, P = 0.001).

PREVENTION OF NEW EXACERBATIONS

1. Participants with new exacerbations during follow-up.

Only one trial (Sellebjerg 1998) including data from 51 participants (14% of participants included in this review) mentioned exacerbation recurrence during follow-up. Both at six months and at one year from randomisation, recurrence of new exacerbations was observed in 17/26 (65%) of those allocated to oral MP and in 13/25 (52%) of those allocated to placebo—a non-significant result.

2. Exacerbation-free time.

No data on this outcome were available from the six trials included in the review .

PREVENTION OF DISABILITY WORSENING

1. Participants worse or unimproved during follow-up.

Only one study (Sellebjerg 1998) reported this outcome. Both at eight weeks and at one year from randomisation, fewer participants were worse off or unimproved in the MP group (9/26, 35% at eight weeks; 13/26, 50% at one year) than in the placebo group (17/25, 68% at eight weeks; 18/23, 78% at one year). However, the results

obtained at one-year follow-up visit could be biased because most of the participants had experienced new exacerbations, and some had started treatment with immunomodulating drugs.

No data were available beyond one year of follow-up to indicate whether steroids had any effect on long-term progression.

2. Mean disability score during follow-up.

No data on this outcome were available from the six trials.

SUBGROUP ANALYSES: INDIRECT COMPARISONS

1. Worse or unimproved within five weeks from randomisation BY DRUG.

Treatments with MP (Durelli 1986; Milligan 1987; Sellebjerg 1998) or with ACTH (Miller 1961a; Rose 1970) were associated with a significant reduction in the risk of being worse or unimproved within five weeks from randomisation, with a greater no significant effect for those given MP. In absolute terms, an additional 394 participants (95% CI 213 to 576) were improved for every 1000 participants treated with MP compared with an additional 190 participants (95% CI 66 to 313 improved) treated with ACTH (Analysis 2.1).

2. Worse or unimproved within five weeks from randomisation BY LENGTH OF TREATMENT.

This indirect comparison was possible only in some trials and showed a slight benefit from short versus long duration of treatment (Analysis 2.2).

This outcome was observed in 3/13 (23%) participants allocated to short-term treatment (five days) with MP and in 6/8 (75%) participants allocated to placebo (Chi^2= 2.28, P = 0.02) (Milligan 1987).
A significant reduction in the risk of this outcome was observed also with long-term MP treatment (15 days): 1/11 (9%) MP participants versus 6/10 (60%) control participants (Durelli 1986) and 12/26 (46%) MP participants versus 19/25 (76%) control participants (Sellebjerg 1998) worsened or unimproved within five weeks from randomisation.

3. Worse or unimproved within five weeks from randomisation BY ROUTE OF ADMINISTRATION.

MP administered intravenously showed some but not a significantly greater effect than oral MP (Analysis 2.3): 3/13 (23%) intravenous MP versus 6/8 (75%) placebo participants (Milligan 1987), 1/11 (9%) intravenous MP versus 6/10 (60%) control participants (Durelli 1986) and 12/26 (46%) oral MP versus 19/25 (76%) control participants (Sellebjerg 1998) had this outcome.

4. Worse or unimproved within five weeks from randomisation BY THE TIME OF START OF TREATMENT FROM EXACERBATION ONSET.

The frequency of this outcome was similarly reduced in participants who received treatment within two weeks in 11/22 (50%) ACTH participants versus 14/18 (78%) placebo participants (Miller 1961a); within four weeks in 12/26 (46%) MP participants versus 19/25 (76%) placebo participants (Sellebjerg 1998); within eight weeks in 1/11 (9%) MP participants versus 6/10 (60%) placebo participants (Durelli 1986); in 3/13 (23%) MP participants versus 6/8 (75%) placebo participants (Milligan 1987); or in 36/103 (35%) ACTH participants versus 49/94 (52%) placebo participants (Rose 1970). However, these comparisons may be confounded by drug and route of administration.

5. Worse or unimproved within five weeks from randomisation BY TYPE OF DISEASE COURSE.

Overall, MP or ACTH showed a protective effect in participants with an RR course at randomisation (Rose 1970; Durelli 1986; Milligan 1987; Sellebjerg 1998). Only one author reported that participants treated during an acute exacerbation that took a progressively worse course did not show a difference compared with control participants (20/33 ACTH participants vs 20/33 placebo participants) (Rose 1970).

ADVERSE EVENTS DURING TREATMENT OR FOLLOW-UP

Side effects or adverse events were reported in four trials only (Rose 1970; Durelli 1986; Milligan 1987; Sellebjerg 1998).

1. Gastrointestinal symptoms.

In the trial with intramuscular ACTH (Rose 1970), peptic ulcer or gastrointestinal bleeding was reported in 1/103 (1%) ACTH and 3/94 (3%) placebo participants. Gastrointestinal bleeding was not reported in the trials using high-dose intravenous MP (Durelli 1986; Milligan 1987), but high-dose oral MP (Sellebjerg 1998) was associated with high risk of gastrointestinal symptoms (OR 5.26, 95% CI 1.46 to 18.94) (Analysis 3.1).

2. Affective disorders including insomnia.

These symptoms were significantly more frequent in MP participants (22%) than in controls (11%). Affective disorders were described as " elevated mood and insomnia" in 5/11 (45%) in the long-term intravenous MP group and in 3/10 (30%) in the control group (Durelli 1986); "psychosis" in 1/9 (11%) in the control group (Milligan 1987); "dysphoria" in 6/26 (23%) in the oral MP group and in 1/25 (4%) in the control group; or "insomnia" in 17/26 (65%) in the MP group and in 2/25 (8%) in the control group (Sellebjerg 1998).

Affective disorders (severe anxiety or severe depression) occurred at an equivalent rate in the ACTH group (2/103; 1%) and in the control group (1/94; 1%) (Rose 1970). The risk for MP was OR 2.37 (95% CI 0.77 to 7.23) and for ACTH 1.79 (95% CI 0.18 to 17.46)—not significant for both drugs.

3. Weight gain and oedema.

These adverse events were reported more often in treated participants (11%) than in controls (2%); however, the ACTH trials greatly accounted for the increased frequency of these adverse events.

4. Hypertension.

In the largest trial (Rose 1970), hypertension developed in 2/103 (2%) in the ACTH group and in none of the participants in the control group. Hypertension was not reported in the three trials with MP (Durelli 1986; Milligan 1987; Sellebjerg 1998).

5. Infection.

Development of infection was never reported in the four trials reporting adverse events.

DISCUSSION

Summary of main results

The primary aim of this review was to determine whether ACTH or corticosteroids reduced short-term disability after an exacerbation, prevented new exacerbations and reduced long-term disability. The secondary aims were to determine whether different drugs or regimens of corticosteroids had different effects.

All six trials included in this review showed a homogeneous pattern suggestive of benefit of ACTH or MP treatment: The probability of amelioration within the first five weeks of treatment was increased by more than 60%, and the mean decline in the EDSS score after one week of therapy was 1.5 points.

This review provides quantitative evidence favouring ACTH or MP against placebo for treating symptoms of an acute exacerbation in patients with multiple sclerosis (Summary of findings for the main comparison).

Evidence was insufficient to allow review authors to determine whether steroids or ACTH treatment prevented new exacerbations and worsening of long-term disability.

The indirect comparisons indicated that MP may confer greater benefit compared with ACTH, and that intravenous MP administration may provide greater effect than oral MP administration in improving the probability of amelioration within the first five weeks of treatment.

Safety data, reported in four trials, indicate gastric disturbances that required symptomatic treatment, affective disorders and insomnia frequently noted after oral MP and hypertension, weight gain and oedema, which were significantly more frequent in the ACTH group than in controls.

Overall completeness and applicability of evidence

Evidence obtained in this review is limited to a small number of included participants (377), 197 (52%) of whom were included in the largest and most influential trial (Rose 1970). We were unsure that randomisation was well conducted in all trials, as allocation concealment was unclearly reported in all studies. In spite of these limitations, no statistically significant heterogeneity was noted for the primary outcome: All trials showed a benefit of ACTH or MP treatment within the first five weeks of treatment. In four trials, the principal outcome measure was the EDSS score, which is commonly used in clinical practice to assess the functional limitations suffered by patients (Durelli 1986; Milligan 1987; Filipovic 1997; Sellebjerg 1998). The EDSS score was between four and six, suggesting that studied relapsing participants did not represent the complete range of disability. In the largest study (Rose 1970), disability was scored by using the DSS scale, and Miller (Miller 1961a) used a subjective evaluation of outcome, with its classification fulfilling the outcome criteria of this review.

The data provide quantitative evidence supporting the use of either drug—ACTH or MP—for the treatment of acute exacerbation in MS patients in reducing short-term disability and hastening recovery.

Evidence was insufficient to allow determination of whether steroids or ACTH treatment prevents new exacerbations and worsening of long-term disability. In fact, only one study (Sellebjerg 1998) (with 51 participants) reported data after one year of follow-up, showing no difference between oral MP and placebo in prevention of new exacerbations or improvement in disability.

The secondary objective of this review was to evaluate whether the effect of treatment of acute exacerbation changed according to different drugs, doses, routes of administration, length of treatment and interval of time between onset of symptoms and start of treatment, and according to course of disease. Evidence was limited because the number of participants was small and only indirect comparisons were undertaken. MP seems to be more effective than ACTH (OR 0.20, 95% CI 0.09 to 0.45 vs OR 0.46, 95% CI 0.28 to 0.77), and intravenous MP administration may provide better benefit than oral MP administration (OR 0.12, 95% CI 0.04 to 0.42vs OR 0.29, 95% CI 010 to 0.89). Regarding the safety profile, gastrointestinal and affective symptoms occurred more frequently in the MP group, and mineral corticosteroid effects were reported in the ACTH group.

As far as length of treatment is concerned, short-term courses of intravenous MP (5 days' treatment with 0.5 to 1 g/d) (Milligan 1987; Filipovic 1997) may confer an equivalent or slightly better benefit than long-term intravenous MP treatment (1 g daily for three days with subsequent taper over 12 days) (Durelli 1986) or long-term oral MP treatment (0.5 g daily for five days with taper over 10 days) (Sellebjerg 1998).

Indirect comparisons by interval of time before the start of treatment from exacerbation onset might suggest that a time interval within 2 to 4 or 8 weeks did not significantly influence the outcome.

We were not able to evaluate the effect of corticosteroids or ACTH on MRI as a surrogate marker of disease activity for lack of data. Measures of MRI were reported in a post hoc study (Sellebjerg 2003) based on subgroups of participants with ON or attacks of MS, as included in two previously published RCTs (Sellebjerg 1998; Sellebjerg 1999b). The OR of improving after one week was better after MP treatment than after placebo and at eight weeks was significantly better only in participants with enhancing lesions on MRI at baseline.

It is widely accepted that during an acute exacerbation of multiple sclerosis, patients should be treated with steroids; because of their role in speeding up recovery (Repovic 2011), intravenous high doses of MP are the most commonly proposed schedule of treatment (Tremlett 1998; Sellebjerg 2005).

Use of ACTH in MS is largely of historical interest. For acute exacerbations, ACTH has mostly been replaced by intravenous MP, with less retention of salt and water and less virilisation. (Schimmer 2001). The safety profile was also confirmed by our data. ACTH rapidly disappears from the circulation after its intravenous administration, and plasma half-life is about 15 minutes. The ACTH labelling information has been recently revised, including information on the treatment of infantile spasms (FDA 2010).

It should be noted that a recent study has proposed the use of ACTH as long-term treatment for MS. This study evaluated the efficacy and safety of monthly pulse ACTH treatment added to β-interferon

for breakthrough MS, compared with pulse MP, in 23 participants. Twelve participants were randomly allocated to open-label ACTH (80 U intramuscularly once per day for 3 consecutive days) and 11 to MP (1 g intravenously in 1 dose) for 12 months. During this time, participants receiving ACTH had fewer relapses than those given MP (Brooks 2013).

Quality of the evidence

The quality of the evidence was scored as moderate for the main outcomes (Summary of findings for the main comparison). One study (Sellebjerg 1998) was considered of low quality because one domain (detection) was at high risk of bias and the number of included participants was low (13% of participants).

Evidence is limited by the small sample of participants.

Randomisation technique and allocation concealment were frequently unclear.

The number of participants excluded and lost to follow-up was small: Overall, only 7 of 377 (2%) participants were excluded from the trials' analyses for any reason. A sensitivity analysis using the worst-case scenario did not change the previous results.

No statistically significant heterogeneity was noted for the primary outcome—treatment of acute exacerbation.

Potential biases in the review process

The updated search did not retrieve new trials.

Agreements and disagreements with other studies or reviews

Two systematic reviews evaluating the efficacy of steroids in the prevention of long-term disability in MS (Ciccone 2008) and comparing intravenous versus oral MP treatment in MS relapses have been published (Burton 2012).

Our results show no definitive conclusion for long-term efficacy of a single pulse steroid treatment: The prevention of new exacerbations was mentioned only in a small trial included in this review (Sellebjerg 1998), which reported a similar outcome in the MP and placebo groups. The Ciccone review (Ciccone 1998) included three trials, all classified as having high risk of bias and including 183 participants (91 treated). Corticosteroid therapy did not reduce the risk of worsening at the end of follow-up (OR 0.51, 95% CI 0.26 to 1.02), but substantial heterogeneity was noted between studies (I^2 = 78.4%). Intravenous periodic high-dose MP was associated with a significant reduction in the risk of disability progression at 5 years in RR MS (OR 0.26, 95% CI 0.10 to 0.66). Oral continuous low-dose prednisolone was not associated with any risk reduction at 18 months (OR 1.23, 95% CI 0.43 to 3.56). The risk of experiencing at least one exacerbation at the end of follow-up was not significantly reduced (OR 0.36, 95% CI 0.10 to 1.25).

Our review suggests that intravenous administration may provide greater effect than oral MP, reducing the risk of worsening at 5 weeks. However, we compared only two studies (42 participants) for intravenous MP and one study (51 participants) for oral administration, and only indirect comparisons were possible. A recent review (Burton 2012) included five studies (215 participants) and compared intravenous versus oral MP treatment. It showed no significant difference in relapse recovery at week four (mean difference -0.22, 95% CI -0.71 to 0.26; P = 0.20) nor differences in MRI activity. However, because only two of the five studies employed more rigorous methodological techniques, the results must be taken with some caution.

AUTHORS' CONCLUSIONS

Implications for practice

It is widely accepted that acute exacerbation in MS patients should be treated with steroids or ACTH (Meyers 1992; Repovic 2011); intravenous high doses of MP are the most commonly used therapy (Tremlett 1998; Sellebjerg 2005). This review provides quantitative evidence favouring ACTH or MP versus placebo for treating acute symptoms of patients with MS.

Overall the data suggest that MP is the most effective drug, and that short-term intravenous administration can be the most appropriate schedule free of relevant adverse effects. Steroids allow recovery from disability if started within 8 weeks from the onset of relapse.

Implications for research

This review gives clear conclusive evidence on the efficacy of steroids versus placebo in the treatment of patients with acute MS relapse. Over the past ten years, no new trials evaluating the effect of steroids versus placebo in this population have been published. Use of corticosteroids is currently the standard treatment for acute MS exacerbation, and trials evaluating their effects versus those of placebo are now unacceptable for ethical reasons.

To answer questions on best schedules of treatment in terms of dosages and timing from relapse onset, systematic reviews comparing different types of steroids and schedules of treatments are warranted. The issue regarding evaluation of clinically relevant outcomes, such as patient-oriented outcome measures and MRI markers of disease activity, remains unresolved. Long-term follow-up is ensured.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Durelli 1986

Methods	Randomised double-blind placebo-controlled trial Italy 1 centre Follow-up = 15 days
Participants	23 participants (MP = 13, placebo = 10) Sex: either Age: 19 to 46 years Included: definite MS (Poser 1983); all RR patients with at least 2 exacerbations in the preceding 3 years and in exacerbation for less than 8 weeks and more than 10 days without spontaneous improvement Excluded: not reported Baseline characteristics: 70% female Mean age: MP = 30.7 years, placebo = 33.9 years Mean EDSS: MP = 5.8, placebo = 5.9 Mean disease duration: MP = 50.8 months, placebo = 67.4 months
Interventions	Rx: MP 15 mg/kg in 500 mL saline daily IV 1st to 3rd days MP 10 mg/kg in 500 mL saline daily IV 4th to 6th days MP 5 mg/kg in 500 mL saline daily IV 7th to 9th days MP 2.5 mg/kg in 500 mL saline daily IV 10th to 12th days MP 1 mg/kg in 500 mL saline daily IV 13th to 15th days Placebo: 500 mL saline daily IV for 15 days All participants received antacids and potassium chloride
Outcomes	Primary outcomes: improvement of one point or more on the EDSS evaluated daily Other clinical outcomes: Time to start of improvement Adverse effects: described
Notes	Recruitment: not reported Supported by: not reported
Risk of bias	

Durelli 1986 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	The authors do not consider this topic
Blinding of participants and personnel (performance bias) All outcomes	High risk	Lumbar puncture was repeated only during steroid treatment and in no case during placebo administration. More side effects and clinical effects in the MP group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double -blind assessment is declared without reporting the method
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawn and lost to follow-up = 2 participants in the MP group because of unblinding. The authors describe 13 participants in the treatment group but refer to results for 12 or 11 in the outcomes tables; no attention to describe the reasons was given
Other bias	Unclear risk	No intention to treat

Filipovic 1997

Methods	Randomised double-blind placebo-controlled trial Serbia 1 centre Follow-up = 7 days
Participants	44 participants (MP = 22, placebo = 22) Sex: not reported Age: 23 to 49 years Included: definite MS (Poser 1983); 17 RR and 23 SP patients in exacerbation Excluded: use of anticholinergic or antidepressive medication; corticosteroid or other immunosuppressive therapy in the last six months; other central nervous system diseases; hearing impairment; emotional and behavioural alterations Baseline characteristics: Mean age: MP = 31.6 years, placebo = 35.3 years Mean EDSS: MP = 4.1, placebo = 4.8 Mean disease duration: MP = 5.1 years, placebo = 5.4 years
Interventions	Rx: MP 1 gr per dose in 500 mL saline daily IV for 5 days Placebo: 500 mL saline daily IV for 5 days
Outcomes	Primary outcome: neurophysiological measure (effects on event-related brain potentials) Other outcome: Clinical outcome: Mean EDSS at 7th day Adverse effects: not reported
Notes	Recruitment: not reported

Filipovic 1997 *(Continued)*

	Supported by: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	The authors do not consider this topic
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Similar behaviour in the groups is described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The data are collected by independent neurologists
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawn and lost to follow-up = 4 participants, because they did not complete only electrophysiological test (MP = 1 participant, placebo = 3 participants)
Other bias	Unclear risk	No intention to treat declared

Miller 1961a

Methods	Randomised double-blind placebo-controlled trial United Kingdom 1 centre Follow-up = 3 weeks
Participants	40 participants (ACTH = 22, placebo = 18) Sex: not reported Included: "unequivocal" MS; 22 RR and 18 PR patients in acute exacerbation of less than 14 days' duration and showing no spontaneous improvement Excluded: not reported Baseline characteristics: Mean age: ACTH = 32.3 years, placebo = 37.4 years Disease duration: not reported
Interventions	Rx: ACTH 60 UI per dose twice daily IM 1st week ACTH 40 UI per dose twice daily 2nd week ACTH 60 UI daily IM on 2nd day, 40 UI daily IM on 4th day, 20 UI daily IM on 6th day of the 3rd week Placebo: saline IM for 21 days All participants received oral potassium chloride 1 gr four times daily Cointervention: physiotherapy
Outcomes	Primary outcome: Improvement/worsening at 3 weeks Adverse events: not reported
Notes	Recruitment: not reported

Miller 1961a *(Continued)*

	Supported by: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	The authors do not consider this topic
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The final evaluation is a judgement of one trained observer who was unaware of the group to which the participant belonged
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawn and lost to follow-up = none
Other bias	Low risk	No intention to treat declared

Milligan 1987

Methods	Randomised double-blind placebo-controlled trial United Kingdom 1 centre Follow-up = 4 weeks
Participants	22 participants (MP = 13, placebo = 9) Sex: either Included: patients with MS according to McDonald and Halliday (1977), in acute exacerbation of less than 8 weeks and showing no spontaneous improvement Excluded: diabetes; severe heart disease; hypertension; pregnancy Baseline characteristics: 82% female Mean age: MP = 33.1 years, placebo = 35.0 years Mean disease duration: 5.4 years Mean EDSS: MP = 5.1, placebo = 4.7
Interventions	Rx: MP 500 mg in 100 mL saline daily IV for 5 days Placebo: 100 mL saline daily IV for 5 days Cointervention: physiotherapy
Outcomes	Primary outcomes: Improvement of one point or more on the EDSS evaluated at 1st and 4th weeks Adverse effects: described
Notes	Recruitment: not reported Supported by: not reported

Milligan 1987 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	The authors do not consider this topic
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clearly described; physiotherapy was given when necessary
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind evaluation is performed only at entry
Incomplete outcome data (attrition bias) All outcomes	Low risk	Wihdrawn and lost to follow -up = 1 participant in the placebo group after becoming psychotic
Other bias	Unclear risk	No intention to treat is declared

Rose 1970

Methods	Randomised double-blind placebo-controlled trial USA 10 centres Follow-up = 4 weeks
Participants	197 participants (ACTH = 103, placebo = 94) Sex: either Included: patients with MS according to Rose (1968); 128 RR and 66 PR in acute exacerbation of less than 8 weeks and showing no spontaneous improvement Excluded: steroids or ACTH therapy in the last three months; unable to follow up because of distance; severe disability (i.e. unable to walk, feed and dress); dementia; concomitant disease (i.e. nervous system diseases, diabetes, severe heart disease; cancer, psychoses, etc.); pregnancy; conditions incompatible with ACTH therapy (i.e. peptic ulcer, renal disease, hypertension, etc.) Baseline characteristics: 61% female Mean age: ACTH = 34.1 years, placebo = 35.4 years Disease duration less than four years: ACTH 38%, placebo 34% Disease duration longer than four years: ACTH 62%, placebo 66% DSS 1 to 3: ACTH 40%, placebo 34% DSS 4 to 5: ACTH 27%, placebo 19% DSS greater than or equal to 6: ACTH 33%, placebo 47%
Interventions	Rx: ACTH 40 UI per dose twice daily IM 1st week ACTH 20 UI per dose twice daily IM for 4 days and ACTH 20 UI daily IM for 3 days 2nd week Placebo: vehicle used for ACTH preparation IM for 14 days
Outcomes	Primary outcomes: Improvement of one point or more on the DSS evaluated at 1st, 2nd, 3rd and 4th weeks

Rose 1970 *(Continued)*

	Adverse events: reported
Notes	Recruitment: April 1965 to July 1968 Supported by a grant to each centre from the National Institute of Neurological Diseases and Blindness and the National Multiple Sclerosis Society

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed at a statistical centre and stratified by centre
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The different frequency and types of adverse effects may reduce the blindness
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	An evaluation of the blindness is performed after the end of the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawn and lost to follow-up = none
Other bias	Low risk	No intention to treat is declared

Sellebjerg 1998

Methods	Randomised double-blind placebo-controlled trial Denmark 1 centre Follow-up = 1 year
Participants	51 participants (MP = 26, placebo = 25) Sex: either Included: definite or probable MS (Poser 1983); all RR in acute exacerbation of less than 4 weeks and showing no spontaneous improvement Excluded: steroid therapy in the last month; interferons or cytotoxic drugs in the last 6 months; pregnancy; lactation; diseases precluding steroids and any degree of spontaneous remission Baseline characteristics: 63% female Median age: MP = 37 years, placebo = 38 years Median disease duration: MP 7 years, placebo 6 years Median EDSS: MP 4.5, placebo 4.0
Interventions	Rx: MP 500 mg per dose daily oral for 5 days MP 400, 300, 200, 100, 64, 48, 32, 16, 8 and 8 mg per dose daily oral on each of the 10 following days Placebo: one identical-looking tablet daily oral for 15 days
Outcomes	Primary outcome: Improvement of one point or more on the EDSS score evaluated at 1st, 3rd and 8th weeks

Sellebjerg 1998 *(Continued)*

	Other clinical outcomes: Recurrent exacerbations at 6 months and 1 year Disability progression at 1 year Adverse events: reported
Notes	Recruited: not reported Supported by grants from the Danish Multiple Sclerosis Society, the Johnsen Memorial Foundation and Pharmacia & Upjohn

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of 10 was performed by the central pharmacy (Copenhagen County Hospitals Services, Herlev, Denmark) using a random numbers table. The randomisation procedures were stratified in two groups according to EDSS score higher or less than 4.5
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Adverse events are more frequent in the treated group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Double-blind method is not described. The outcomes are also subjective measures Participants received scores from the same person throughout the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant's treatment was discontinued after 7 days
Other bias	Low risk	No intention to treat is described

ACTH: adrenocorticotrophic hormone.
DSS: Disability Status Scale.
EDSS: Expanded Disability Status Scale.
IM: intramuscular.
IV: intravenous.
MP: methylprednisolone.
PR: progressive relapsing.
RR: relapsing-remitting.
Rx: treatment.

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

Study	Reason for exclusion
Barkhof 1991	Case series study of 12 patients treated with high-dose intravenous methylprednisolone. Results of MRI changes before and after treatment are reported
Beretta 1997	Case series study of 27 patients treated with high-dose methylprednisolone. Clinical results after treatment are reported

Study	Reason for exclusion
Boman 1966	This is a double-blind RCT of the effects of ACTH treatment in 25 patients with chronic forms of MS. Selected patients were not in acute exacerbation
Buckley 1982	Case series study of 6 patients treated with high-dose methylprednisolone during an acute exacerbation
Burnham 1991	The authors studied the effects of high-dose intravenous methylprednisolone on MRI lesions in 7 patients with acute demyelinating diseases
Ciccone 1998	Selected patients not in acute exacerbation (i.e. without exacerbations for at least 45 days before randomisation)
Compston 1987	Laboratory measurements are compared in paired samples from 50 patients included in an RCT of methylprednisolone in the treatment of multiple sclerosis. No clinical outcomes are reported
Dong 2012	Comparative RCT without placebo group
Dowling 1980	Case series study of seven patients treated with intravenous methylprednisolone followed by oral prednisone
Frequin 1993	The authors studied 67 patients with multiple sclerosis treated with high-dose intravenous methylprednisolone and determined the effects of the treatment on lymphocytes and lymphocyte subpopulations in the cerebrospinal fluid and peripheral blood
Frequin 1994	Follow-up of 56 patients treated with high-dose intravenous methylprednisolone because of symptomatic deterioration
Goodkin 1998	This RCT compared the tolerability and efficacy of two doses of intravenous methylprednisolone in patients with secondary progressive MS. No placebo arm
Gunal 1996	No double-blind trial. The outcome measure was progression prevention
Hoogervorst 2002	The authors examined the MRI effect (cerebral volume changes) of steroid treatment administered to all MS patients participating in a clinical trial of oral interferon beta
Hoogstraten 1990	This study is an RCT of the long-term effects of ACTH treatment of acute relapse in 29 MS patients. It is not a double-blind study. Outcome results are unclear
Kesselring 1989	Case series study of 50 patients treated with high-dose intravenous methylprednisolone. MRI results are reported.
Kiessling 1987	Patients not in acute phase
Kupersmith 1994	Historical review
Marforio 1984	This is a double-blind CCT of the effects of ACTH treatment in 44 MS patients. The author was unable to provide outcome data
Martin 1964	Patients not in acute phase
Martinez-Caceres 2002	The authors studied 16 patients with multiple sclerosis treated with high-dose intravenous methylprednisolone and determined the effects of the treatment on lymphocytes and lymphocyte subpopulations in the peripheral blood before and after treatment
Merritt 1954	Case series study of 42 patients treated with ACTH

Study	Reason for exclusion
Millar 1967	This is an RCT of the effects of ACTH treatment in 181 MS patients treated with ACTH daily for 18 months. It is not a double-blind study. Selected patients are not in acute exacerbation. The authors do not report the duration of treatment in the placebo group
Miller 1961b	This study is a three-arm RCT comparing prednisolone daily for 18 months with solprin and placebo. Selected patients (86) are not in acute exacerbation
Miller 1992	The authors studied the effects of high-dose intravenous methylprednisolone on MRI lesions in 10 MS patients during acute relapses
Newman 1982	This study is a retrospective analysis of 61 MS patients treated with methylprednisolone during a deterioration in their symptoms
Repovic 2004	Review
Rinne 1968	This is a double-blind RCT on the effects of ACTH treatment of both progressive (37) and relapsing-remitting MS patients (36) during acute exacerbations. Disability is measured by Alexander's scoring system (1961). We were unable to extract outcome data
Rumbach 1990	Case series study comparing 17 patients treated with high-dose methylprednisolone during an acute exacerbation and 13 patients clinically stable who received no treatment
Schweingruber 2011	Review
Sellebjerg 1999b	RCT of oral high-dose methylprednisolone compared with placebo in patients with acute optic neuritis
Then Bergh 2001	RCT evaluating the neuroendocrine effect of cotreatment with the antidepressant moclobemide as an adjunct to oral corticosteroids in MS
Tourtellotte 1965	Patients not in acute exacerbation
Tourtellotte 1980	Case series study. ACTH gel and corticosteroids were given to 28 MS patients to determine whether de novo central nervous system IgG synthesis could be eradicated
Trotter 1980	Case series study of immunological parameters in 12 MS patients treated with high dose of methylprednisolone
Versino 1994	Case series study. The authors studied eye movements in 24 patients with MS before and after high-dose methylprednisolone infusions
Visser 2004	RCT add-on active treatments. Patients were randomly assigned to 500 mg IVMP directly followed by 0.4 g/kg IVIg or placebo (2% human albumin) for five consecutive days
Whitaker 1993	Case series study. Determination of the levels of myelin basic protein-like material in cerebrospinal fluid of MS patients treated with glucocorticoids
Zivadinov 2001	RCT comparing regular pulses of intravenous methylprednisolone with intravenous methylprednisolone at the same dose schedule only for relapses

MS: multiple sclerosis.
MRI: magnetic resonance imaging.
RCT: randomised controlled trial.
CCT: controlled clinical trial.

DATA AND ANALYSES

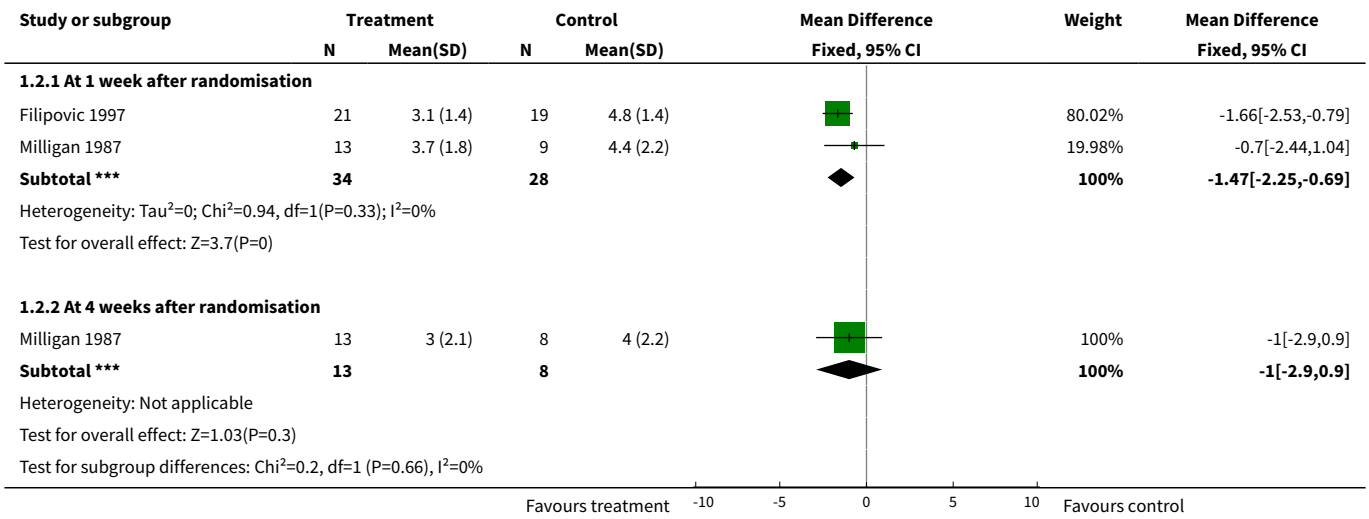
Comparison 1. Corticosteroids or ACTH versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Worse or unimproved within 5 weeks from randomisation	5	330	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.24, 0.57]
2 Mean disability (EDSS) score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At 1 week after randomisation	2	62	Mean Difference (IV, Fixed, 95% CI)	-1.47 [-2.25, -0.69]
2.2 At 4 weeks after randomisation	1	21	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.90, 0.90]
3 Patients with new exacerbations during follow-up	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 At 6 months	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [0.57, 5.19]
3.2 At 1 year	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [0.57, 5.19]
4 Worse or unimproved during follow-up	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 At 8 weeks	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.09, 0.80]
4.2 At 1 year	1	49	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.10, 0.96]

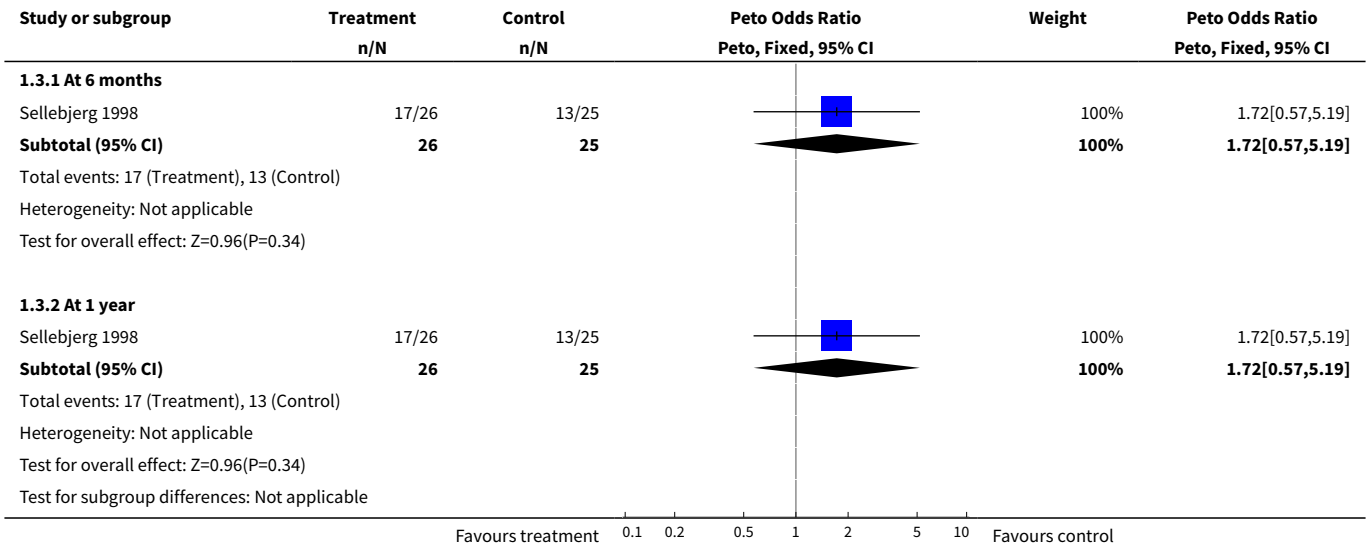
Analysis 1.1. Comparison 1 Corticosteroids or ACTH versus placebo, Outcome 1 Worse or unimproved within 5 weeks from randomisation.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Durelli 1986	1/11	6/10		6.08%	0.11[0.02,0.66]
Miller 1961a	11/22	14/18		11.84%	0.31[0.09,1.12]
Milligan 1987	3/13	6/8		6.34%	0.13[0.02,0.75]
Rose 1970	36/103	49/94		60.31%	0.5[0.28,0.87]
Sellebjerg 1998	12/26	19/25		15.42%	0.29[0.1,0.89]
Total (95% CI)	**175**	**155**		**100%**	**0.37[0.24,0.57]**
Total events: 63 (Treatment), 94 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.36, df=4(P=0.36); I^2=8.3%					
Test for overall effect: Z=4.51(P<0.0001)					

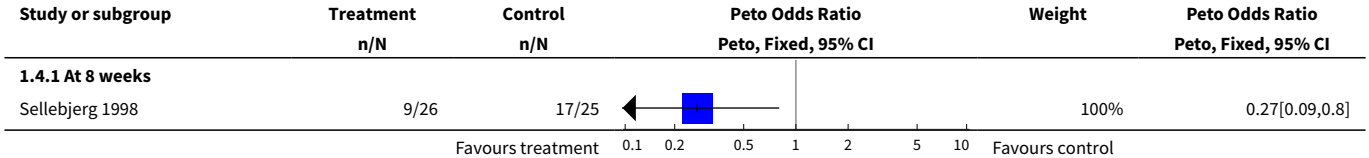
Analysis 1.2. Comparison 1 Corticosteroids or ACTH versus placebo, Outcome 2 Mean disability (EDSS) score.

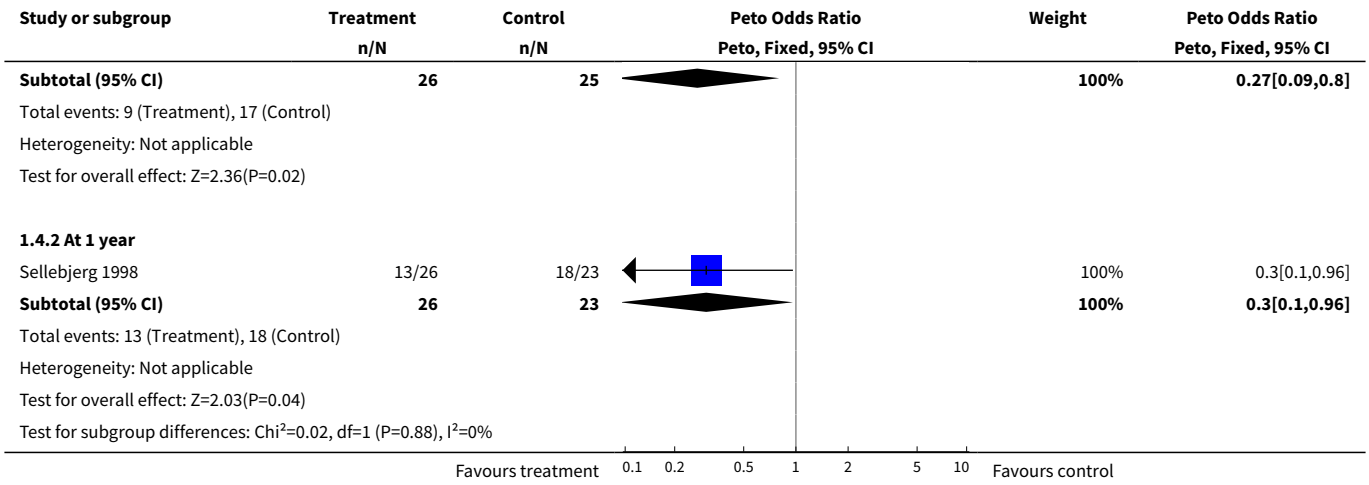


Analysis 1.3. Comparison 1 Corticosteroids or ACTH versus placebo, Outcome 3 Patients with new exacerbations during follow-up.



Analysis 1.4. Comparison 1 Corticosteroids or ACTH versus placebo, Outcome 4 Worse or unimproved during follow-up.





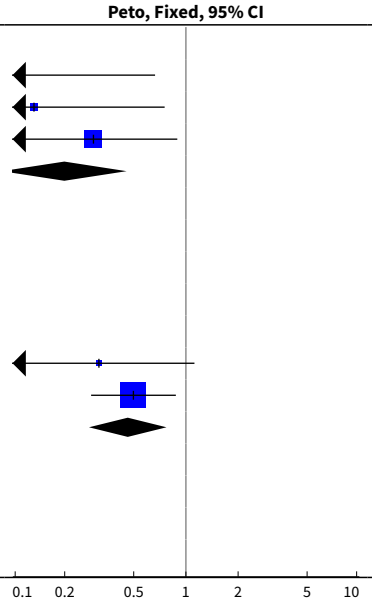
Comparison 2. Corticosteroids or ACTH versus placebo; indirect comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Worse or unimproved within 5 weeks from randomisation BY DRUG	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Methylprednisolone versus placebo	3	93	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.20 [0.09, 0.45]
1.2 ACTH versus placebo	2	237	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.28, 0.77]
2 Worse or unimproved within 5 weeks from randomisation BY LENGTH OF TREATMENT	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Methylprednisolone: short treatment (5 days)	1	21	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.02, 0.75]
2.2 Methylprednisolone: long treatment (15 days)	2	72	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.09, 0.57]
3 Worse or unimproved within 5 weeks from randomisation BY ROUTE OF ADMINISTRATION	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Oral methylprednisolone	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.29 [0.10, 0.89]
3.2 Intravenous methylprednisolone	2	42	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.04, 0.42]
4 Worse or unimproved within 5 weeks from randomisation BY TIME TO START OF TREATMENT FROM EXACERBATION ONSET	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Within 2 weeks	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.31 [0.09, 1.12]
4.2 Within 4 weeks	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.29 [0.10, 0.89]
4.3 Within 8 weeks	3	239	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.39 [0.23, 0.65]

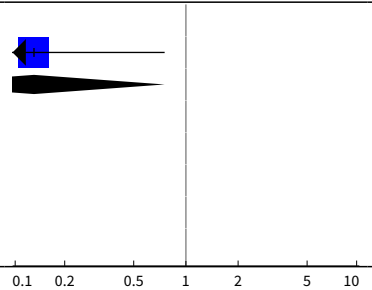
Analysis 2.1. Comparison 2 Corticosteroids or ACTH versus placebo; indirect comparisons, Outcome 1 Worse or unimproved within 5 weeks from randomisation BY DRUG.

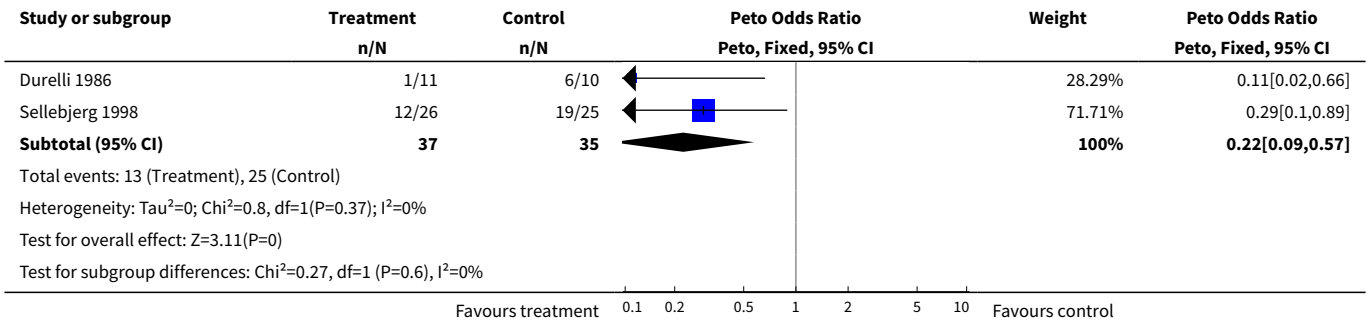
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.1.1 Methylprednisolone versus placebo					
Durelli 1986	1/11	6/10		21.85%	0.11[0.02,0.66]
Milligan 1987	3/13	6/8		22.76%	0.13[0.02,0.75]
Sellebjerg 1998	12/26	19/25		55.39%	0.29[0.1,0.89]
Subtotal (95% CI)	**50**	**43**		**100%**	**0.2[0.09,0.45]**
Total events: 16 (Treatment), 31 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.07, df=2(P=0.59); I^2=0%					
Test for overall effect: Z=3.82(P=0)					
2.1.2 ACTH versus placebo					
Miller 1961a	11/22	14/18		16.42%	0.31[0.09,1.12]
Rose 1970	36/103	49/94		83.58%	0.5[0.28,0.87]
Subtotal (95% CI)	**125**	**112**		**100%**	**0.46[0.28,0.77]**
Total events: 47 (Treatment), 63 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=1(P=0.52); I^2=0%					
Test for overall effect: Z=2.94(P=0)					
Test for subgroup differences: Chi^2=2.88, df=1 (P=0.09), I^2=65.24%					



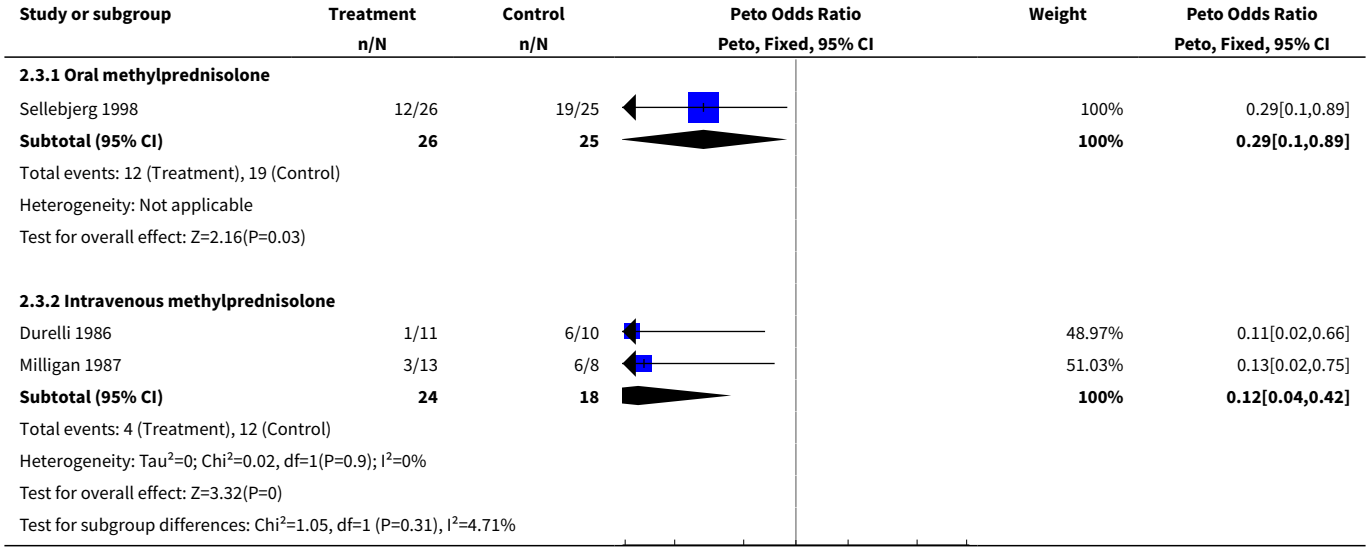
Analysis 2.2. Comparison 2 Corticosteroids or ACTH versus placebo; indirect comparisons, Outcome 2 Worse or unimproved within 5 weeks from randomisation BY LENGTH OF TREATMENT.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.2.1 Methylprednisolone: short treatment (5 days)					
Milligan 1987	3/13	6/8		100%	0.13[0.02,0.75]
Subtotal (95% CI)	**13**	**8**		**100%**	**0.13[0.02,0.75]**
Total events: 3 (Treatment), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.28(P=0.02)					
2.2.2 Methylprednisolone: long treatment (15 days)					

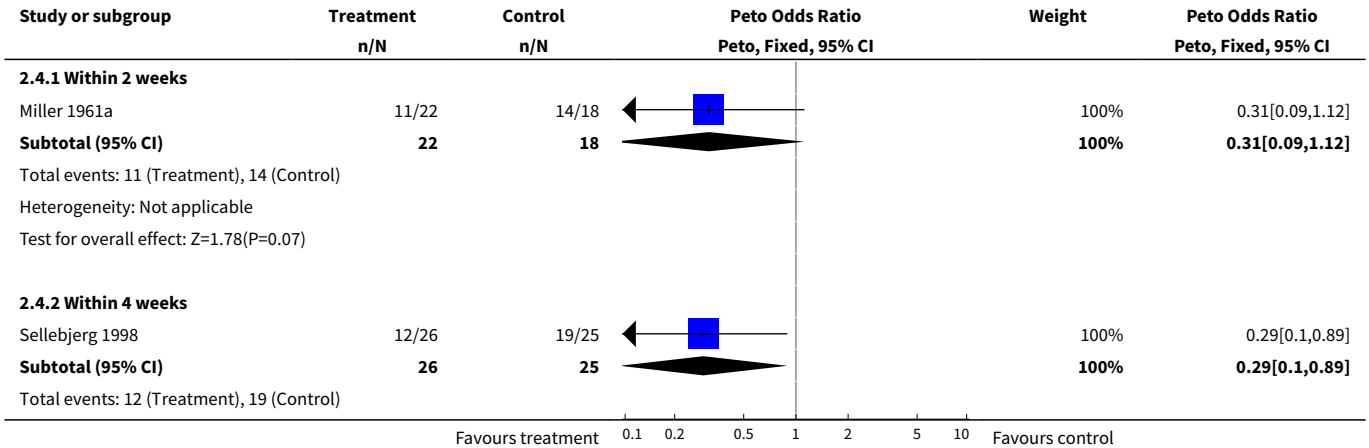


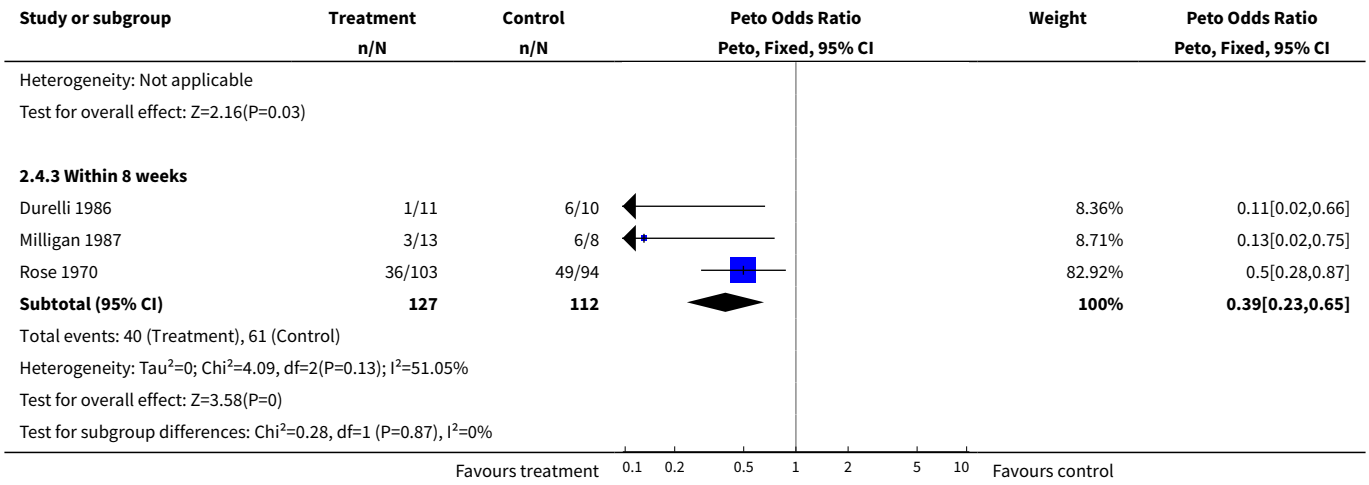


Analysis 2.3. Comparison 2 Corticosteroids or ACTH versus placebo; indirect comparisons, Outcome 3 Worse or unimproved within 5 weeks from randomisation BY ROUTE OF ADMINISTRATION.



Analysis 2.4. Comparison 2 Corticosteroids or ACTH versus placebo; indirect comparisons, Outcome 4 Worse or unimproved within 5 weeks from randomisation BY TIME TO START OF TREATMENT FROM EXACERBATION ONSET.

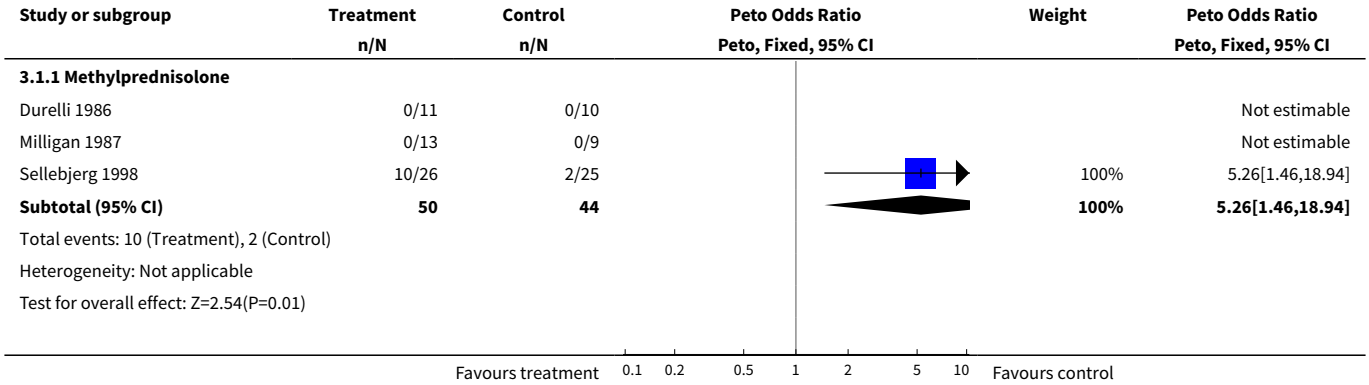


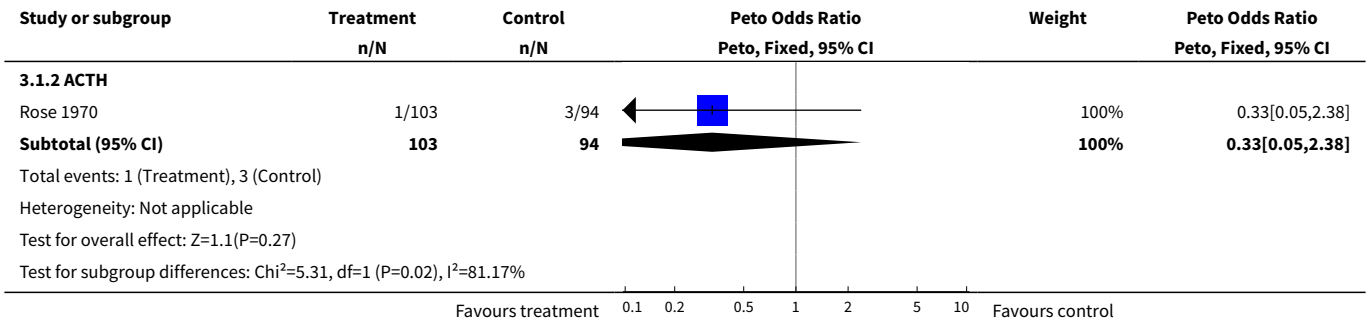


Comparison 3. Adverse events during treatment or follow-up

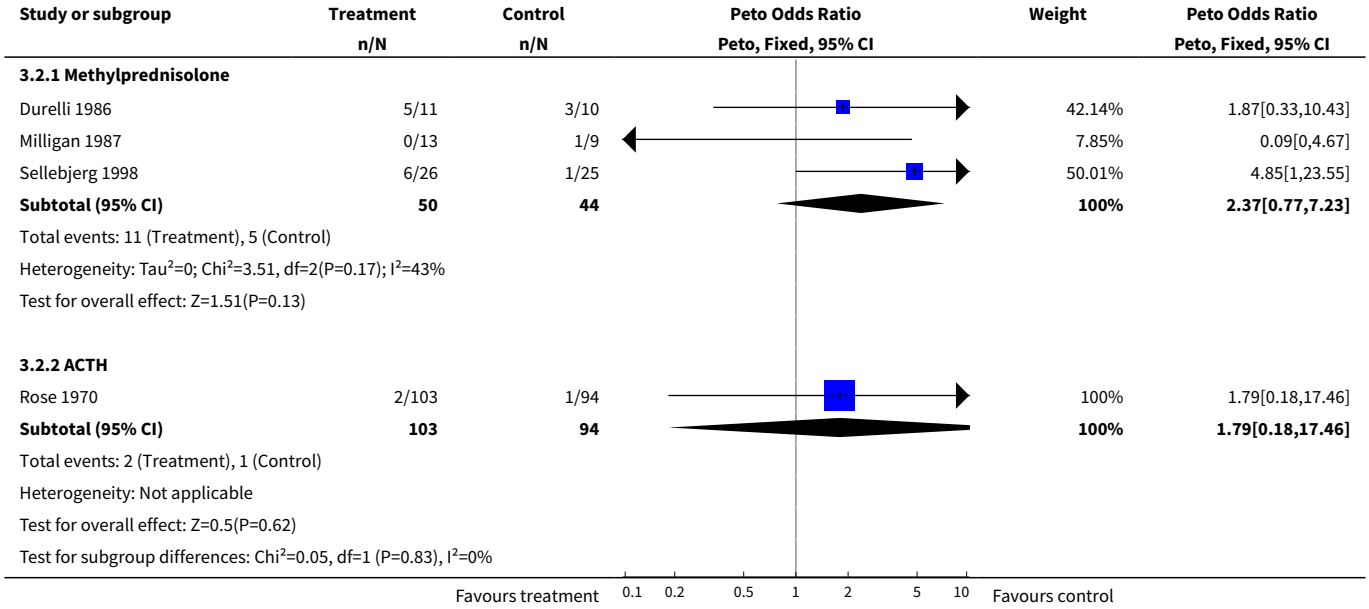
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gastrointestinal bleeding by drug	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Methylprednisolone	3	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.26 [1.46, 18.94]
1.2 ACTH	1	197	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.05, 2.38]
2 Psychic disorders by drug	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Methylprednisolone	3	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.37 [0.77, 7.23]
2.2 ACTH	1	197	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.79 [0.18, 17.46]

Analysis 3.1. Comparison 3 Adverse events during treatment or follow-up, Outcome 1 Gastrointestinal bleeding by drug.





Analysis 3.2. Comparison 3 Adverse events during treatment or follow-up, Outcome 2 Psychic disorders by drug.



APPENDICES

Appendix 1. Keywords

{adrenal cortex hormones} OR {steroids} OR {methylprednisolone} OR {prednisolone} OR {dexamethasone} OR {corticosteroids} OR {acth} OR {prednisone} OR {Adrenocorticotropic Hormone} OR {steroid} OR {Adrenocorticotropin} OR {adrenocorticotrophic hormone} OR {6-methylprednisolone} OR {corticotrophin} OR {corticotropin}

WHAT'S NEW

Date	Event	Description
30 April 2013	Review declared as stable	No evidence of further research interest in this area was found
30 April 2013	Amended	Risk of bias tables, SOF tables and a flow diagram of the retrieved literature have been added. The Review team has changed

Date	Event	Description
31 March 2013	New search has been performed	Search strategy rerun

HISTORY

Protocol first published: Issue 1, 1999
Review first published: Issue 4, 2000

Date	Event	Description
30 June 2008	Amended	Converted to new review format.
30 October 2002	New search has been performed	Searches were re-run
29 October 2002	New citation required but conclusions have not changed	No new RCTs were identified

CONTRIBUTIONS OF AUTHORS

All authors of the first version contributed to conceiving the idea, developing the research questions and designing the protocol. Dr G Filippini and Dr F Brusaferri appraised the relevance and validity of the papers and abstracted data. Dr A Citterio wrote to drug companies to ask about unpublished studies. She cross-checked abstracted data and arbitrated in discussions to resolve disagreements between the two review authors. G Filippini analysed the results and wrote the text of the review.

For the present review, Dr A Citterio and Dr L La Mantia assessed the retrieved studies for their eligibility and updated the paper accordingly. All review authors critically reviewed the whole manuscript.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Fondazione I.R.C.C.S.- Istituto Neurologico Carlo Besta, Italy.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The planned outcomes “Exacerbation free time” and “Mean disability score during follow -up” were not evaluated because no data were available.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenocorticotropic Hormone [*therapeutic use]; Anti-Inflammatory Agents [*therapeutic use]; Glucocorticoids [*therapeutic use]; Methylprednisolone [*therapeutic use]; Multiple Sclerosis [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans