

# Corticosteroids for the long-term treatment in multiple sclerosis (Review)

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[Intervention Review]

# Corticosteroids for the long-term treatment in multiple sclerosis

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## ABSTRACT

### Background

Short term high dose corticosteroid treatment improves symptoms and short term disability after an acute exacerbation of multiple sclerosis (MS) but it is unknown whether its long-term use can reduce the accumulation of disability.

### Objectives

To determine the efficacy and safety of long-term corticosteroid use in MS.

### Search methods

We searched The Cochrane MS Group Trials Register (February 2007), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2007, Issue 1), MEDLINE (1966 to February 2007) and EMBASE (1980 to February 2007). In an effort to identify further published, unpublished and ongoing trials we searched reference lists and contacted trial authors and one pharmaceutical company.

### Selection criteria

We considered controlled, randomised trials (RCTs), with or without blinding, of long term treatment (i.e. longer than 6 months) of any type of corticosteroid in MS, irrespective of disease course.

### Data collection and analysis

Reviewers independently assessed trial quality and extracted data. Study authors were contacted for additional information.

### Main results

Three trials, all classified at high risk of bias, contributed to this review (Miller 1961; BPSM 1995; Zivadinov 2001) resulting in a total of 183 participants (91 treated). Corticosteroid therapy did not reduce the risk of being worse at the end of follow-up (odds ratio [OR] 0.51, 95% confidence interval [CI] 0.26 to 1.02) but there was a substantial heterogeneity between studies ( $I^2$ : 78.4%). *I. v.* periodic high dose methylprednisolone (MP) was associated with a significant reduction in the risk of disability progression at 5 years in relapsing-remitting (RR) MS (OR 0.26, 95% CI 0.10 to 0.66), while oral continuous low dose prednisolone was not associated

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with any risk reduction in disability progression at 18 months (OR 1.23, 95% CI 0.43 to 3.56). Risk of experiencing at least one exacerbation at end of follow-up was not significantly reduced with corticosteroid treatment (OR 0.36; 95% CI 0.10 to 1.25).

Only one study recorded adverse events: in one patient i. v. MP was discontinued after the fourth pulse when he developed acute glomerulonephritis; a second patient was removed from the study after the fifth i. v. MP pulse because of severe osteoporosis.

### Authors' conclusions

There is not enough evidence that long-term corticosteroid treatment delays progression of long term disability in patients with MS. Since one study at high risk of bias showed that the administration of pulsed high dose i. v. MP is associated with a significant reduction in the risk of long term disability progression in patients with RR MS, an adequately powered, high quality RCT is needed to investigate this finding.

## PLAIN LANGUAGE SUMMARY

### The long-term use of anti-inflammatory corticosteroids for treating multiple sclerosis

Multiple sclerosis is an inflammatory disease affecting the brain and spinal cord. It results in episodes of neurological deficit which recover (relapses) as well as accumulation of sustained disability with the passage of time. Corticosteroids are potent anti-inflammatory drugs. It is postulated that long-term use of steroids may reduce the accumulation of disability. The reviewers found three studies addressing this issue. A meta-analysis showed a trend towards a beneficial effect of long-term corticosteroids on accumulation of disability; however only two small studies contributed to this result. It was not possible to reliably comment on the effect of long-term corticosteroids on the frequency of relapses. Side effects were poorly documented. Therefore rigorous randomised controlled trials of this treatment are warranted.

## BACKGROUND

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system whose aetiology is still unknown. Treatment is based on the assumption that autoimmunity plays a major role in the pathogenesis of disease (Compston 2002; Rizvi 2004a; Rizvi 2004b; Frohman 2005).

Corticosteroids inhibit lymphocyte proliferation and the synthesis of most known proinflammatory cytokines and cell surface molecules required for immune function with a mechanism that involves a specific corticosteroid receptor (Sloka 2005). Because of their potent anti-inflammatory effects, corticosteroids have been used to treat MS patients since the 1950s and today are considered the standard treatment for acute exacerbations (Compston 2002; Rizvi 2004b; Frohman 2005). However, corticosteroids, being immunosuppressive drugs, might prevent or delay the occurrence of future episodes of inflammatory demyelination (Gold 2001).

A previous Cochrane review showed that a short term high dose intravenous methylprednisolone (i. v. MP) course within 8 weeks of acute exacerbation of MS, improved symptoms and short term disability without significant side effects but data were insufficient to estimate the effect on prevention of new exacerbations and

reduction of long term disability (Filippini 2000). In the present review we wanted to consider long term corticosteroid treatment to specifically prevent disease progression rather than to treat acute exacerbations.

The idea that corticosteroids might prevent new exacerbations, reduce long term disability, and therefore modify the natural history of MS, comes from several observations:

- the initial results of the Optic Neuritis Treatment Trial suggested that treatment of a first episode of optic neuritis with a single course of i. v. MP followed by a tapering course of oral prednisone, reduced the 2 year rate of development of clinically definite MS (Beck 1993), although this effect was lost on further follow-up extending to 4 years (Beck 1995);
- a phase II randomised controlled trial (RCT) in relapsing-remitting (RR) MS comparing the efficacy of repeated pulsed i. v. MP with i. v. MP at the same dosage regimen but administered only for relapses, showed that pulsed i. v. MP slowed the development of destructive lesions (T1 black holes), the rate of whole-brain atrophy progression and the development of sustained physical disability (Zivadinov 2001);

- another phase II RCT of bimonthly i. v. MP pulses in patients with secondary progressive (SP) MS showed a beneficial effect on time to onset of sustained progression of disability with the high-dose regimen (Goodkin 1998a);
- one non randomised trial with historical controls suggested that patients with MS treated with high dose i. v. corticosteroids during six months post-partum might reduce the childbirth-associated risk of acute exacerbation (de Seze 2004);
- some studies indicated that pulsed i. v. MP produced a rapid and dose dependent reduction in gadolinium enhancement on cerebral MRI that lasted for up to 6 months (Gasperini 1997; Goodkin 1998b; Smith 1993; Barkhof 1994).

In a systematic review (Brusaferrri 2000) that included around 500 randomised patients comparing the effects of adrenocorticotrophic hormone (ACTH), prednisolone or MP (with or without azathioprine) versus placebo, no significant effect on long-term disability and relapse prevention was noted. However this meta-analysis included studies in which these agents were given for as little as 5-30 days. The review also reported the occurrence of both minor and major side effects, the latter including severe Cushing's syndrome, hypertension, herpes simplex, herpes zoster, severe ankle oedema, femoral fracture and gastrointestinal bleeding, but these occurred with ACTH or an azathioprine/methylprednisolone combination (Brusaferrri 2000).

Pulsed regimens of administration have renewed interest in corticosteroids as they are reported to be well-tolerated and safe, with only minor and dose-related side effects, such as insomnia, transient mood disorders, acneiform-rash, heartburn, headache and myalgias (Pozzilli 2004). The rationale for repeated pulsed administration is based on the hypothesis that these drugs may have a long-lasting immunosuppressive effect, as indicated by the above mentioned studies, and that MS may be a restless, progressive disease even when, as in the RR form, the clinical course between two exacerbations is stable (Stone 1995).

Thus, a systematic review of RCT to gather all data available to date on long term use of corticosteroids appeared worthwhile.

## OBJECTIVES

The objective of this review was to determine whether long term treatment of MS patients with corticosteroids:

- 1) prevents or significantly delays disability progression at long term follow-up;
- 2) reduces the risk of exacerbations, increasing the proportion of relapse-free patients during follow-up;
- 3) is well tolerated and safe.

We selected progression of disease rather than the occurrence of exacerbations as the primary outcome measure, both because the frequency of exacerbations does not necessarily correlate with clinical evidence of disease progression (Confavreux 2000), a more meaningful parameter than the occurrence of symptoms and signs that can remit, and because we also wanted to consider progressive forms of the disease.

We also wanted to evaluate the effect of different doses, drugs, routes of administration, regimens (i.e. pulsed or continuous), length of treatment and whether the effect of treatment was different according to types of disease (relapsing/remitting, relapsing/progressive [RP], secondary progressive or primary progressive [PP]).

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We planned to consider all apparently unconfounded RCTs, with or without blinding, of long term treatment with corticosteroids in MS.

#### Types of participants

Patients with definite MS according to clinical and paraclinical diagnostic criteria (Poser 1983; McDonald 2001; Polman 2005) irrespective of their disease course (RR, RP, SP or PP). Studies describing only clinical criteria were accepted as well (McDonald 1977).

#### Types of interventions

Active treatment: long term courses (i.e. longer than 6 months) of any type of corticosteroid, continuous or intermittent, provided that they were not started for relapses (i.e. started more than 2 months after a relapse), whatever the administration route and dosage.

Control: placebo or no treatment. Short courses (i.e. maximum 21 days of duration) of corticosteroids were permitted, provided they were administered for relapses.

#### Types of outcome measures

##### Primary outcomes

##### Efficacy

We studied the following outcome measures in either treatment group at 1 and 2 years and at the end of the scheduled follow-up period:

#### *Primary outcome*

1. Patients who progressed. Whenever unspecified, progression was defined as a persistent worsening of at least one point in EDSS (Kurtzke 1983), recorded whilst not in relapse. However, other definitions of progression were accepted, including a persistent half-point increase starting from EDSS score 5.5, as is often reported in the literature.

#### **Safety**

Safety outcome was assessed among primary endpoints by unique measures incorporating all events occurring throughout the trials:

1. Number of patients with severe side effects. If not otherwise specified, side effects were defined as severe when leading to one of the following: death, hospitalisation, treatment discontinuation.
2. Extraction of any available information about safety in both corticosteroid and control groups.

#### **Secondary outcomes**

2. Patients experiencing at least one exacerbation, which was defined as the acute or subacute appearance/reappearance of neurological signs and symptoms for at least 24 hours, in the absence of fever or infection.
3. Relapse free survival, if available.

#### **Search methods for identification of studies**

One reviewer (FB) provided references pertinent to this review already retrieved in the course of two previous systematic reviews on corticosteroids for multiple sclerosis which he had co-authored (Brusaferrri 2000; Filippini 2000). The same search strategy was used in this review to update searches.

#### **Electronic searches**

The search strategy we used was drawn from the one developed by the Multiple Sclerosis Group.

Relevant trials were identified searching the following sources:

1. The Cochrane MS Group Trials Register (February 2007)
2. The Cochrane Central Register of Controlled Trials (The Cochrane Library 2007, Issue 1)(Appendix 1)
3. MEDLINE (January 1998 - February 2007)(Appendix 2)
4. EMBASE (1998 - February 2007)(Appendix 3)

Papers in any language were accepted provided they met the criteria specified above.

#### **Searching other resources**

4. Reference lists of studies on corticosteroid treatment for MS

5. Abstracts of neurological and multiple sclerosis congresses and symposia, conference proceedings, dissertations and other forms of reports where trials relevant to the review are likely to have been published

6. We searched for unpublished studies by contacting researchers who were known to be involved in this field

7. We contacted Pfizer Inc, who had acquired Upjohn, a company which was known to have an interest in the use of steroids in MS, in order to identify any unpublished data.

#### **Data collection and analysis**

##### **Selection of studies**

The contact reviewer (AC) divided the search results between co-reviewers (SB, FB, IG, CS and AP) who decided separately which articles to retrieve. Abstracts of references with titles of interest were examined to determine relevance. When the abstract suggested relevance, or relevance was unclear from the abstract, or where no abstract was available, a copy of the article was obtained. Copies of articles identified in reference lists of papers related to the use of corticosteroid treatment in MS were also obtained. Trained reviewers (AC and FB) verified that the papers thus selected adhered to the inclusion criteria. AC and FB were not blinded to the names of the authors, their institutions, the journal, or the journal publisher. Disagreements were resolved by discussion between the two reviewers.

All studies meeting the inclusion criteria were summarized in the table Characteristics of Included Studies.

##### **Assessment of methodological quality**

Each reviewer (AC, SB, FB, IG, AP and CS) separately extracted information, for each included trial, regarding the method of randomisation, blinding of outcome evaluators, and whether all the randomised patients were accounted for in the analysis. One reviewer (AC) contacted the authors of the trials if the above information was not available in the published reports. In the case of an unpublished study (BPSM 1995) this information was extracted from the protocol approved by local Ethics Committee in 1995. Since two reviewers (AC and SB) had a leading role in such study, they did not participate to the assessment of methodological quality. Reviewers assessed the quality of the trials independently and were asked to fill in a form shown in Table 1 that was then sent to the contact reviewer (AC). Concealment of allocation (telephoning to a central office, first entering the data into a computer, the pharmacy, using identical numbered containers, or sequential, sealed, opaque envelopes), blinding in outcome evaluation and intention-to-treat analysis were evaluated and graded as present, absent or unclear. The included studies were categorised into one of three quality categories (protection against bias), based on those described in the Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 (section 6.7.1): A (low risk of bias, all of the criteria present), B (moderate risk of bias, one or more criteria unclear), C (high risk of bias, one or more criteria absent) (Higgins

2005). We planned to summarise the interobserver agreement in the overall quality score using the weighted kappa statistic.

#### Data extraction

All the reviewers (AC, SB, FB, IG, AP and CS) independently extracted data for outcome and safety assessments according to measures defined in the 'Types of outcome measures' section, filling a form shown in Table 2. Forms were then sent to the contact reviewer (AC) who summarized the data. The same forms were used to ask original authors for unpublished data.

We planned to use intention-to-treat analysis, extracting the number of patients originally allocated to each treatment group irrespective of compliance. When numbers extracted by two or more reviewers varied, differences were resolved by discussion.

#### Data analysis

The efficacy analyses were based on the results of the individual trials for disability at one year or more after treatment initiation and the safety analyses on the results for severe side effects. The analyses on secondary outcomes and on minor side effects were used to support the data on primary outcomes. A weighted estimate of the treatment effects across trials (odds ratio) was calculated using a fixed effect model. For interpreting the results, 95% confidence intervals were used. Heterogeneity across studies was quantified using  $I^2$ , i.e. by describing the percentage of the variability in the effect estimates that is due to heterogeneity rather than sampling error. A value greater than 50% was considered substantial heterogeneity. (Higgins 2002)

#### Sensitivity analyses

If patients were excluded or lost to follow up after randomisation, further information was sought by correspondence with the trialists. If the data about these patients remained unavailable, a worst-case scenario analysis for the outcome of "disability progression" was undertaken to ensure significance of the results. In this analysis, it was assumed that those patients who were lost to follow up in the treatment group had the worst outcome while those patients who were lost to follow up in the control group had the best outcome. We planned to make a definite conclusion about the treatment effectiveness if the effects of primary and worst-case meta-analyses were in the same direction and magnitude.

#### Subgroup analyses

If substantial heterogeneity was found on efficacy analysis, we planned to explore this heterogeneity using the following subgroup analyses:

- (1) comparison of trials with quality A with trials with quality B or C;
- (2) comparison of the efficacy of treatment in patients treated within one year versus those treated after one year of MS onset;
- (3) comparison of the effect of different doses, drugs, routes of administration, regimens (i.e. intermittent or continuous) and length of treatment;
- (4) comparison of the efficacy of treatment in RR, RP, SP or PP patients

We planned to use the overlap of the confidence intervals of the summary estimates in the groups of comparison (lack of overlap between confidence intervals indicating statistical significance).

## RESULTS

### Description of studies

We identified 2270 articles (previous systematic reviews 111; CENTRAL 170; MEDLINE 1741; EMBASE 242 ; hand searching 4; unpublished 2; drug manufacturers zero).

Ten possible RCTs involving long-term administration of steroids in MS were selected by reviewers on the basis of inclusion criteria after reading the abstracts. We excluded seven studies after reading the full published papers: one study was a dose-comparison trial of i. v. MP without a control group (Goodkin 1998a), two studies used MRI parameters as outcome measures (Pato-Pato 2003; Then Bergh 2006), one study was a case series with a historical control group (de Seze 2004), two studies were uncontrolled case series (Beretta 1997; Pirko 2004); one study was a comparison with vitamin B12 (Tourtellotte 1965). (See table of excluded studies). In total three trials contributed to this review: Miller 1961, BPSM 1995 and Zivadinov 2001.

#### Data availability

One study was unpublished (BPSM 1995) because it was prematurely interrupted for organisational problems and lack of funding. This study's data were made available by one of the reviewers (SB) and checked by a second reviewer (CS). The other two RCTs were published as full papers. However, since the exact number of patients with disability worsening and experiencing exacerbations during follow-up could not be extracted from the Zivadinov 2001 paper, this information was obtained by contacting the authors.

#### Type of interventions and patients

Both the BPSM 1995 and Zivadinov 2001 studies used pulsed high dose i. v. MP in RR MS whilst the study by Miller 1961 used continuous oral prednisolone in patients with "slowly progressive", "fluctuant" and "rapidly progressive" MS (diagnostic criteria were not given). Patients in the control group were allowed to be treated with corticosteroids in case of exacerbation in two studies (BPSM 1995; Zivadinov 2001) but in one of them (BPSM) the occurrence of a relapse automatically ended the study for individual patients (see "Outcomes definition" in this paragraph for further details). Treatment duration was 18 months in the Miller 1961 study, 5 years in the Zivadinov 2001 study and two years or until the first relapse in the BPSM 1995 (see table of included studies).

#### Baseline characteristics

Equivalence between the treatment and control group in the baseline participants' characteristics was present in the three selected RCTs.



### Outcomes definition

- The [Miller 1961](#) study used different clinical outcome measures (see table of characteristics of included studies). To extract data on progression of disability we used the reported number of patients who “deteriorated” at the “patients’ own assessment” at 18 months (that outcome was divided in “improved”, “deteriorated” and “remained unchanged” in the paper), making due allowance for the potential biases involved in such definition. “Acute exacerbation” was not defined and data was reported for individual relapses rather than for the number of patients experiencing at least one exacerbation. Since we could not get further clarification about acute relapses in the Miller study we could not consider such study for analysis on prevention of new exacerbations.

- In the [BPSM 1995](#) study, progression of disability was defined but patients were not followed-up after the first exacerbation, contrary to what was planned. Since patients not experiencing a relapse in the two years of the study were just 2, we did not have any data on long-term disability progression for the majority of the patients.

- The [Zivadinov 2001](#) study defined progression of disability as at least a 1.0-point worsening from baseline for patients who entered at or below an EDSS score of 5.0 or a 0.5-point worsening from baseline for patients who entered at an EDSS score of 5.5. Worsening was required to persist for at least two consecutive 4-month visits during the first 3 years of the study or at least two consecutive 6-month visits during the fourth and fifth years of the study. Relapses were defined as the appearance or reappearance of one or more symptoms, attributable to MS, accompanied by objective deterioration on neurologic examination, lasting at least 24 hours, in the absence of fever, preceded by neurologic stability for at least 30 days and in the absence of steroid withdrawal within 60 days of the new event.

### Risk of bias in included studies

#### Randomisation and concealment allocation

The method of randomisation was centralised, providing adequate concealment of allocation in two trials ([BPSM 1995](#); [Zivadinov 2001](#)): in the [BPSM 1995](#) study randomisation and allocation were generated by computer by personnel not involved in patients management and in the [Zivadinov 2001](#) study this was done by a statistician “who had no contact with the study subjects”. In the [Miller 1961](#) the method of randomisation was classified as “unclear” by all the reviewers independently, since the method of randomisation was not described.

#### Blinding

The [BPSM 1995](#) and [Miller 1961](#) studies were double blinded. During the [Zivadinov 2001](#) study blindness to treatment of patients and clinical examiners was not warranted (although participants did not know the allocation group into which they will have been allocated at the randomisation step); radiologists conducting image analysis were blinded.

Intention-to-treat analysis, excluded and losses to follow-up

An intention-to-treat analysis was impossible for all the three trials. In the [BPSM 1995](#) study the intention to treat analysis was planned but not performed and there were 10 patients (7 treated) lost to follow-up (28% overall). Moreover, patients experiencing an exacerbation were not followed up although a two year follow-up was planned. In the [Zivadinov 2001](#) and [Miller 1961](#) trials a total of 11 participants (7% overall) were excluded after randomisation or lost to follow-up (see details in table of included studies). No information was available on the outcome measures in these participants.

#### Overall assessment of validity

The three included RCTs were classified at high risk of bias (see table of included studies).

The inter-observer agreement in the overall quality score was not summarised with the kappa statistic since there was a 100% agreement among the reviewers.

### Effects of interventions

A total of 183 (91 treatment, 92 control) out of 210 randomised participants were considered (27 patients assigned to calcium aspirin in the [Miller 1961](#) study were excluded from the analysis).

#### PREVENTION OF DISABILITY WORSENING (PRIMARY OUTCOME)

(1) at the end of follow up

Data from 2 trials ([Miller 1961](#); [Zivadinov 2001](#)) with 136 participants, 74% of participants included in the review) were available on this outcome. Corticosteroid therapy was associated with a non significant reduction in the risk of being worse at the end of follow-up (odds ratio [OR] 0.51, 95% confidence interval [CI] 0.26 to 1.02). There was substantial heterogeneity between the two trials ( $I^2$ : 78.4%).

(2) at the end of follow up: sensitivity analysis

Since information on patients excluded and lost to follow-up was unavailable, a worst case scenario was carried out as pre-specified. Such analysis, performed by considering patients who were randomised to treatment and then excluded as worst outcome events, did not significantly change the result (number of events in treated = 30/72; number of events in controls = 37/75; OR 0.74, 95% CI 0.39 to 1.41) and confirmed the inconsistency across the two studies ( $I^2$ : 73.7%).

(3) at one year

Only data from the [Zivadinov 2001](#) study was available, on 81 patients. Corticosteroid therapy was associated with a non significant reduction in the risk of being worse at 1 year of follow-up (OR 0.16, 95% CI 0.02 to 1.38).

(4) at one year: sensitivity analysis

Sensitivity analysis of the 88 patients originally randomised did not change the result (OR 0.86, 95% CI 0.24 to 3.04).

(5) at two years

Only data from the [Zivadinov 2001](#) study was available, on 81 patients. Corticosteroid therapy was associated with a significant



reduction in the risk of being worse at 2 years of follow-up (OR 0.09, 95% CI 0.02 to 0.42). In absolute terms this means that 330 patients for every 1000 treated (95% CI 170 to 490) avoided disability progression after two years of treatment.

(6) at two year: sensitivity analysis

Treatment was still associated with a favourable outcome in the worst case scenario (OR 0.29, 95% CI 0.10 to 0.85).

(7) subgroup analysis

Subgroup analysis was performed since there was substantial heterogeneity after efficacy analysis on disability progression at the end of follow-up. Such analysis should be regarded as a qualitative rather than quantitative description, since the RCTs considered were just two (Miller 1961; Zivadinov 2001). Taking into account the pre-specified issues for subgroup analyses, the two trials did not differ for quality but they did for type of drug (MP versus prednisolone respectively), route of administration (i. v. versus oral), regimen (intermittent versus continuous), length of treatment (5 years versus 1 year and a half), disease course (RR versus variable course), disability progression definition (objective versus patients' own assessment in the Miller 1961 study) and mean disease duration before entry into the study (6 years versus 12 years).

I. v. 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) (Zivadinov 2001), while oral continuous low dose prednisolone was not associated with any risk reduction in disability progression at 18 months (OR 1.23, 95% CI 0.43 to 3.56) (Miller 1961).

In absolute terms, 320 patients for every 1000 treated with pulsed high dose i. v. MP (95% CI 110 to 520) avoided long term disability progression according to the Zivadinov study.

PREVENTION OF NEW EXACERBATION (SECONDARY OUTCOME)

(1) At the end of follow-up

Data from two trials (BPSM 1995; Zivadinov 2001) with 107 participants (59% of participants included in the review) was available on this outcome. Risk of experiencing at least one exacerbation was not significantly reduced with corticosteroid treatment (OR 0.36; 95% CI 0.10 to 1.25). No substantial heterogeneity across studies was observed ( $I^2$ : 0%).

(2) At one year

Data was available from two trials (BPSM 1995; Zivadinov 2001) with 115 patients. Corticosteroid therapy did not change the risk of new exacerbations (OR 1.17, 95% CI 0.57 to 2.43).

(3) At two years

Data was available from two trials (BPSM 1995; Zivadinov 2001) with 107 patients. Corticosteroid therapy did not change the risk of new exacerbations (OR 1.48, 95% CI 0.61 to 3.59).

(4) Exacerbation-free time

No data was available from the 3 trials included in the review on this outcome.

ADVERSE EVENTS

(1) Severe adverse events

In the Miller 1961, study adverse events were poorly described and two patients allocated corticosteroids were withdrawn because of hypertension. No other severe adverse effects were reported in either treatment group.

In the Zivadinov 2001, study 2 patients dropped out in the pulsed i. v. MP arm: in one, i. v. MP was discontinued after the fourth pulse when the patient developed acute glomerulonephritis; the second patient was removed from the study after the fifth i. v. MP pulse because of severe osteoporosis. Twenty-five patients in the i. v. MP arm and 18 patients in the control arm were followed up 21 months after the study with bone mineral densitometry: a further patient in the pulsed i. v. MP arm and one in the control arm developed osteoporosis (Zorzon 2005). There were no fractures throughout the study.

In the BPSM 1995 study no severe adverse effects were reported but 7 out of 19 patients (37%) in the pulsed i. v. MP arm versus 3 out of 17 in the control arm (18%) dropped out for unspecified reasons.

(2) Minor adverse events

Almost all patients treated with i. v. MP in the Zivadinov 2001 study experienced "metallic taste" after the bolus. Insomnia, pyrosis, anxiety, constipation, acneiform rash, and polyphagia were frequently reported in both treated and control groups and did not require treatment.

In the Zivadinov 2001 study the following long term events that did not require discontinuation of the planned therapy were reported without specifying the treatment group: osteoporosis (2 patients), arterial hypertension (1 patient), and recurrent herpetic infections (1 patient).

In the BPSM 1995 study careful monitoring of minor adverse events was also planned but not performed.

In the Miller 1961 study minor adverse events were not reported.

## DISCUSSION

### Progression of disability

A meta-analysis was not possible for this outcome at one or two years since data was unavailable. Meta-analysis of two studies for this outcome at the end of follow up showed a trend towards a significant effect in favour of steroids, but it is possible that the substantial heterogeneity between studies diluted the effect of one of them. Indeed, on the basis of the Zivadinov 2001 study, periodic high dose i. v. MP significantly prevents progression of long term disability in patients with RRMS. To quantify the result in terms of number needed to treat, 3 patients (95% CI 2 to 9) need to be treated to avoid disability progression in one. This result seems quite robust as the effects of primary and worst-case meta-analyses are in the same direction and magnitude. The effect of i. v. MP

is evident from the second year of treatment and is maintained at least until the fifth year of treatment.

As opposed to pulsed high dose i. v. MP, continuous low dose treatment with oral prednisolone did not show any effect neither on disability progression nor on prevention of new exacerbations.

Different hypotheses could be formulated to explain the difference in results between the [Miller 1961](#) and [Zivadinov 2001](#) studies: (a) different drug type (i. v. methylprednisolone in the [Zivadinov 2001](#) study and oral prednisolone in the [Miller 1961](#) study), (b) the different length of treatment (5 years in the [Zivadinov 2001](#) study and 18 months in the [Miller 1961](#) study), (c) different cumulative dose of steroid (23.04g of i. v. methylprednisolone in the [Zivadinov 2001](#) study and oral prednisolone equivalent to 5.28g oral methylprednisolone in the [Miller 1961](#) study, over the first 18 months of both studies), (d) different regimens (pulsed in the [Zivadinov 2001](#) study and continuous in the [Miller 1961](#) study), (e) the different type of disease (RR course in the [Zivadinov 2001](#) study and various courses in the [Miller 1961](#) study), (f) difference in mean disease duration before entry into the study (6 years in the [Zivadinov 2001](#) study and 12 years in the [Miller 1961](#) study), (g) different ethnic background (Italian in the [Zivadinov 2001](#) study and English in the [Miller 1961](#) study), (h) a  $\beta$  type error (i.e. incapability of identifying a difference that exists) due to low sample size in the [Miller 1961](#) study, (i) lack of blinding in the [Zivadinov 2001](#) study, (j) different definition of disability progression (objective assessment in the [Zivadinov 2001](#) study and patients' own assessment in [Miller](#) study), (k) a combination of a, b, c, d, e, f, g, h, i and/or j. A dose-dependent effect might well be operative since in a trial comparing 2 doses of i. v. MP pulses in patients with secondary progressive MS, a relative beneficial effect on time to onset of sustained progression of disability was observed with the high-dose regimen compared with the low dose ([Goodkin 1998a](#)). Although in our analysis the beneficial effect of i. v. MP was first detected after two years of treatment, in the [Zivadinov 2001](#) study the beneficial effect of pulsed i. v. MP became evident after 8 months of treatment, as shown by the time survival curve to onset of sustained EDSS score worsening; therefore an effect after 8 months of therapy should have also been visible in the [Miller 1961](#) study, if everything else was equal.

The use of corticosteroid therapy in the control group in the [Zivadinov 2001](#) study could be another cause of heterogeneity. However, this should have hampered rather than favoured the effect of corticosteroid in the active treatment group in the [Zivadinov 2001](#) study.

### Prevention of acute exacerbation

The secondary objective of this review was to evaluate the effect of treatment on prevention of acute exacerbations. Although one more RCT could be included ([BPSM 1995](#)) for this analysis, many patients were lost to follow up in this study. I. v. MP did not protect against the occurrence of relapses during the period studied.

[the available evidence was extremely weak since many patients were lost to follow up in this study. Data was not sufficient to determine the effect of corticosteroid treatment on prevention of exacerbations; alternatively it could well be that long-term corticosteroids do not prevent exacerbations.]

### Adverse events

Only one study ([Zivadinov 2001](#)) included in this review formally recorded adverse events following corticosteroid treatment but the list may be incomplete; consequently the lack of evidence cannot be construed as paucity of adverse events.

Oral corticosteroids cannot be administered continuously at cumulative doses equivalent to pulsed regimens because of side effects mostly osteoporosis ([Zorzon 2005](#)). This, together with the negative results from the [Miller 1961](#) study, shift the risk-to-benefit ratio against continuous oral corticosteroid therapy. Compared to pulsed i. v. MP, there is therefore less evidence favouring further study in RCTs. As regards periodic high dose i. v. MP, although it emerged as effective from the present review, routine use in clinical practice is not yet indicated because the evidence comes from a single small study that was classified at high risk of bias and was not open to intention-to-treat analysis. Therefore the evidence cannot be considered conclusive but rather suggestive of possible efficacy. Larger RCTs of pulsed i. v. MP are warranted. Due to the reported lack of difference between oral and i. v. routes of equivalent high doses of methylprednisolone ([Alam 1993](#)), RCTs of pulsed oral high dose MP are also warranted.

## AUTHORS' CONCLUSIONS

### Implications for practice

There is no enough evidence to justify the routine use of long term corticosteroids treatment for MS patients. This is because only three trials, all classified at high risk of bias, contributed to this review.

### Implications for research

This review is suggestive of a favourable effect of long term use of pulsed high dose i. v. MP that could modify the disease course in RR MS patients. Since it is possible that such an effect is statistically and clinically significant without severe adverse effects as compared to other treatments like interferon beta ([Rice 2001](#)) or mitoxantrone ([Martinelli 2005](#)), a large and high quality randomised controlled trial is urgently needed to test the efficacy of pulsed high dose i. v. MP.

No marketing interest may economically sustain the execution of RCTs on corticosteroids today. Moreover the planning of placebo-controlled RCTs may be considered unethical when drugs for the treatment of MS are available. Therefore, the comparison of pulsed

high dose i. v. MP plus a disease modifying drug versus a disease modifying drug alone could be an option.

## ACKNOWLEDGEMENTS

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### BPSM 1995

Methods	C = randomisation by computer. Double-blind. Losses to follow-up: 10 (7 assigned MP).
Participants	Single centre in Italy; 36 patients with RR clinically definite MS (Poser 1983 criteria); no relapse in the previous 45 days; EDSS < 5.5. 21 (58%) female Mean age 35yr.
Interventions	Rx: i.v. MP 2 g in saline solution for 12 hours, every 45-60 days, for two years or until relapse Control: i.v. saline solution at the same schedule
Outcomes	Probability of remaining relapse free (primary end point) Disability reduction after two years Safety
Notes	Prematurely interrupted at 36 out of 72 planned patients for organisational reasons and lack of funding. Quality C: high risk of bias (concealment of randomisation: present, blinding in outcome evaluation: present; intention-to-treat analysis: absent [planned but not performed])

#### *Risk of bias*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

#### Miller 1961

Methods	C = not described. Double-blind. Losses to follow-up: 7 (3 assigned Prednisolone, 1 on "dummy" tablets and 3 on calcium aspirin)
Participants	Single center in UK; 86 patients with "slowly progressive", "fluctuant" and "rapidly progressive" MS (diagnostic criteria not described). 47 (55%) female Mean age 33yr.
Interventions	Rx: 29 patients on oral prednisolone tablets 15 mg/day for 8 months then 10 mg/day for 10 months Rx: 27 patients on 9 calcium aspirin tablets (54 g)/day Control: 30 patients on a correspondent number of "dummy" tablets

**Miller 1961** (Continued)

Outcomes	Average change in Alexander score Functional grades at 6 and 18 months Acute exacerbations Patients' own assessment at 18 months	
Notes	Quality C: high risk of bias (concealment of randomisation: unclear, blinding in outcome evaluation: present; intention-to-treat analysis: absent)	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Allocation concealment?	Unclear risk	B - Unclear

**Zivadinov 2001**

Methods	C = treatment assignment generated by statistician who had no contact with study subjects. Single-blind. Losses to follow up: 7 (4 assigned MP). No intention-to-treat analysis.	
Participants	Single center in Italy; 88 patients with RR clinically definite MS (Poser 1983 criteria); without exacerbation or progression and steroid treatment in the previous 3 months; EDSS < or = 5.5. 60 (68%) female Mean age 32yr.	
Interventions	Rx: i.v. MP 1 g/day for 5 days with an oral prednisone taper (day 6 and 7 50 mg, day 8 and 9 25 mg), every 4 months for 3 years, and every 6 months for the subsequent 2 years Control: i.v. MP, same dose schedule, only for relapses	
Outcomes	Primary outcome measure: MRI parameters (T2 and T1 lesion volume and brain parenchymal volume changes); secondary outcomes: disability progression and relapses	
Notes	Quality C: high risk of bias (concealment of randomisation: present, blinding in outcome evaluation: absent (radiologists blinded but clinical examiners unblinded); intention-to-treat analysis: absent)	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Allocation concealment?	Low risk	A - Adequate

C: concealment of allocation  
RR: relapsing remitting  
MS: multiple sclerosis



Rx: Treatment  
i.v.: intravenous  
MP: methylprednisolone

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

Study	Reason for exclusion
Beretta 1997	Retrospective study on a series of cases
de Seze 2004	Not randomised (series of patients in post-partum period; historical control group)
Goodkin 1998a	No control group with placebo or no treatment (randomised controlled trial of two different dose of bimonthly i. v. MP pulses)
Pato-Pato 2003	No control group (series of cases). No outcome measures useful for this meta-analysis
Piazza 2000	Uncompleted, confounding randomised trial comparing interferon beta 1b to interferon beta 1b plus MP
Pirko 2004	No control group (series of cases).
Then Bergh 2006	Not randomised single-cross-over study with no outcome measures useful for this meta-analysis
Tourtellotte 1965	Confounding randomised trial comparing oral MP with cyanocobalamin: 30 patients in cyanocobalamin group had been treated with ACTH during the trial

i.v.: intravenous  
MP: methylprednisolone

## DATA AND ANALYSES

### Comparison 1. Corticosteroids versus placebo or open control

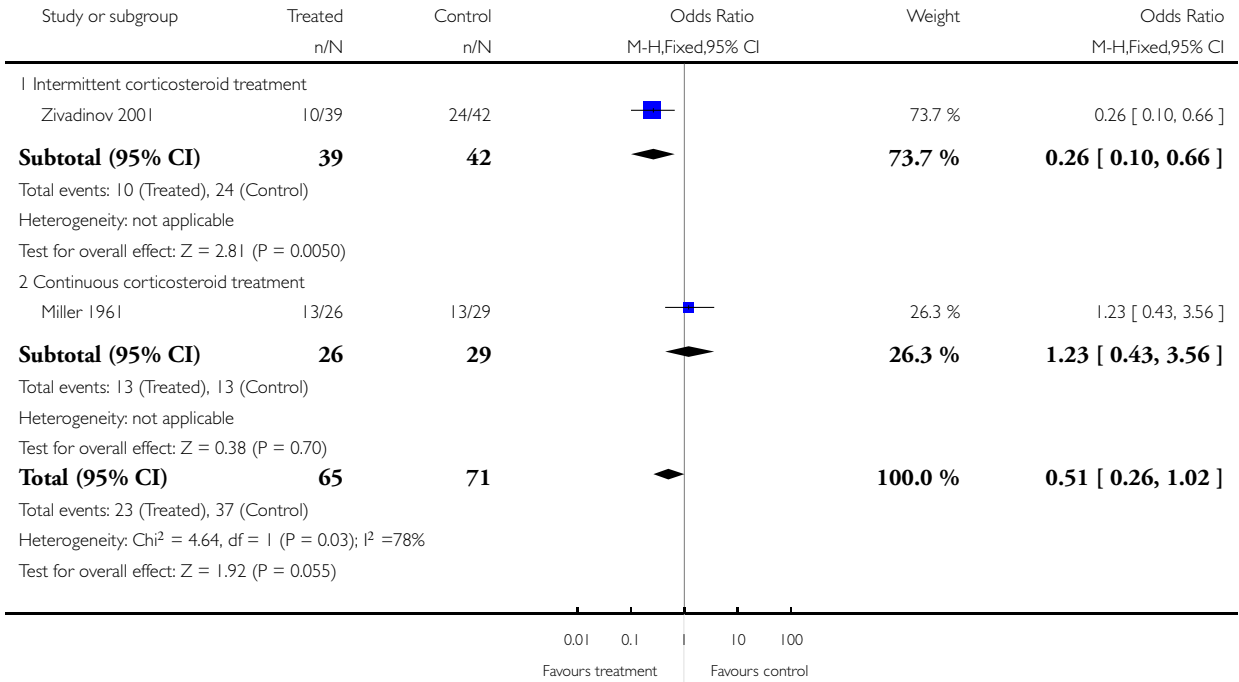
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disability progression at end of follow-up	2	136	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.26, 1.02]
1.1 Intermittent corticosteroid treatment	1	81	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.10, 0.66]
1.2 Continuous corticosteroid treatment	1	55	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.43, 3.56]
2 Disability progression at end of follow-up: sensitivity analysis	2	147	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.39, 1.41]
2.1 Intermittent corticosteroid treatment	1	88	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.18, 1.00]
2.2 Continuous corticosteroid treatment	1	59	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [0.58, 4.50]
3 Disability progression at year 1	1	81	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.38]
4 Disability progression at year 1: sensitivity analysis	1	88	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.24, 3.04]
5 Disability progression at year 2	1	81	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.02, 0.42]
6 Disability progression at year 2: sensitivity analysis	1	88	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.10, 0.85]
7 New exacerbations at end of follow-up	2	107	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.10, 1.25]
8 New exacerbations at year 1	2	115	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.57, 2.43]
9 New exacerbations at year 2	2	107	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [0.61, 3.59]

**Analysis 1.1. Comparison 1 Corticosteroids versus placebo or open control, Outcome 1 Disability progression at end of follow-up.**

Review: Corticosteroids for the long-term treatment in multiple sclerosis

Comparison: 1 Corticosteroids versus placebo or open control

Outcome: 1 Disability progression at end of follow-up

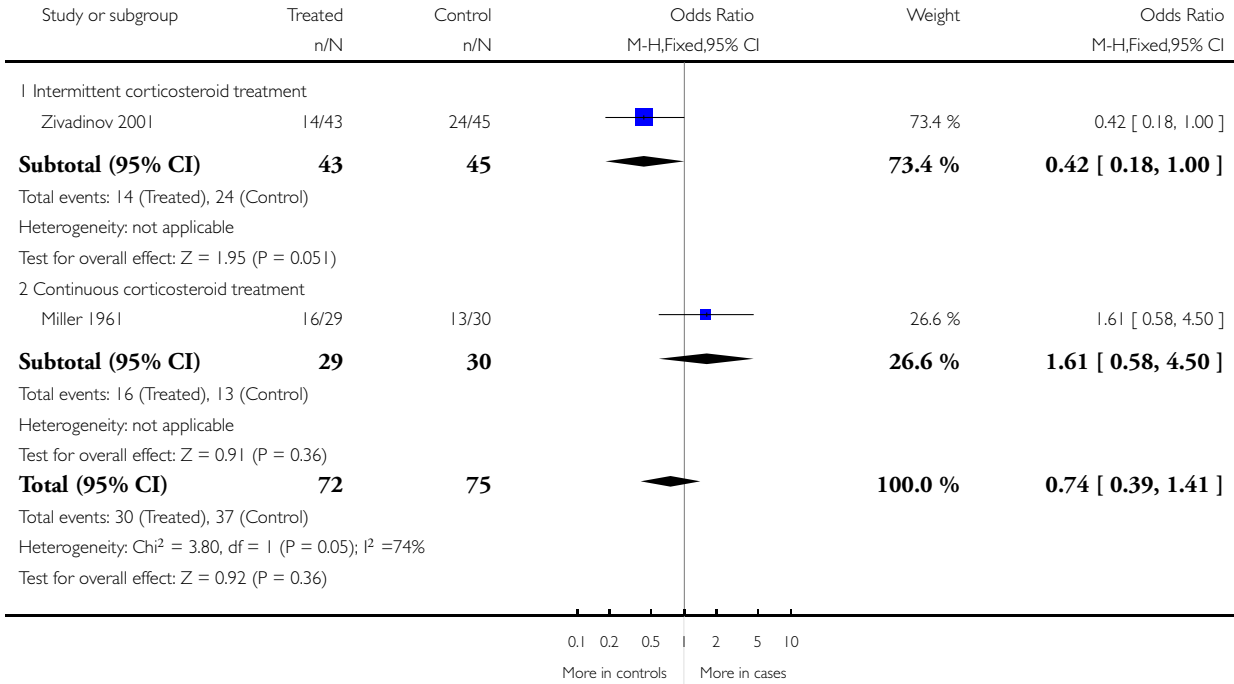


**Analysis 1.2. Comparison 1 Corticosteroids versus placebo or open control, Outcome 2 Disability progression at end of follow-up: sensitivity analysis.**

Review: Corticosteroids for the long-term treatment in multiple sclerosis

Comparison: 1 Corticosteroids versus placebo or open control

Outcome: 2 Disability progression at end of follow-up: sensitivity analysis

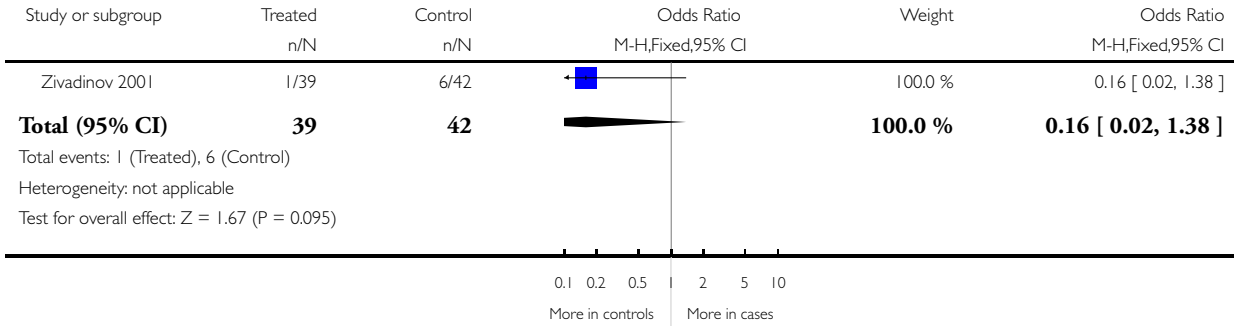


### Analysis I.3. Comparison I Corticosteroids versus placebo or open control, Outcome 3 Disability progression at year I.

Review: Corticosteroids for the long-term treatment in multiple sclerosis

Comparison: I Corticosteroids versus placebo or open control

Outcome: 3 Disability progression at year I

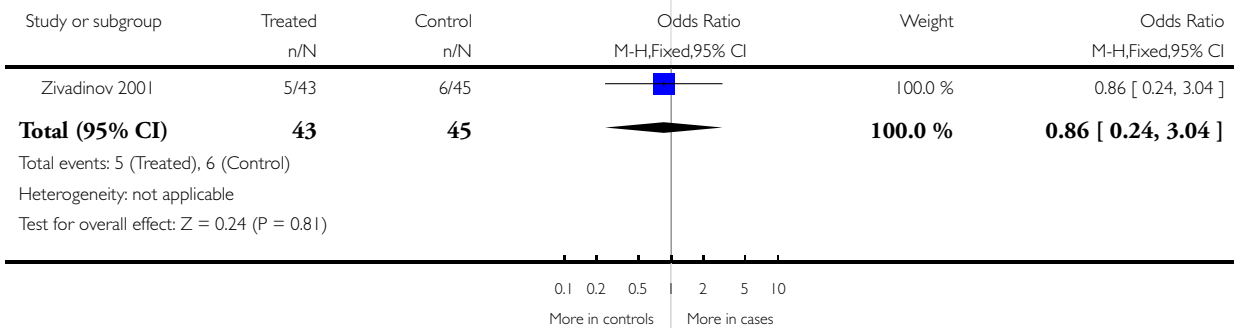


### Analysis I.4. Comparison I Corticosteroids versus placebo or open control, Outcome 4 Disability progression at year I: sensitivity analysis.

Review: Corticosteroids for the long-term treatment in multiple sclerosis

Comparison: I Corticosteroids versus placebo or open control

Outcome: 4 Disability progression at year I: sensitivity analysis

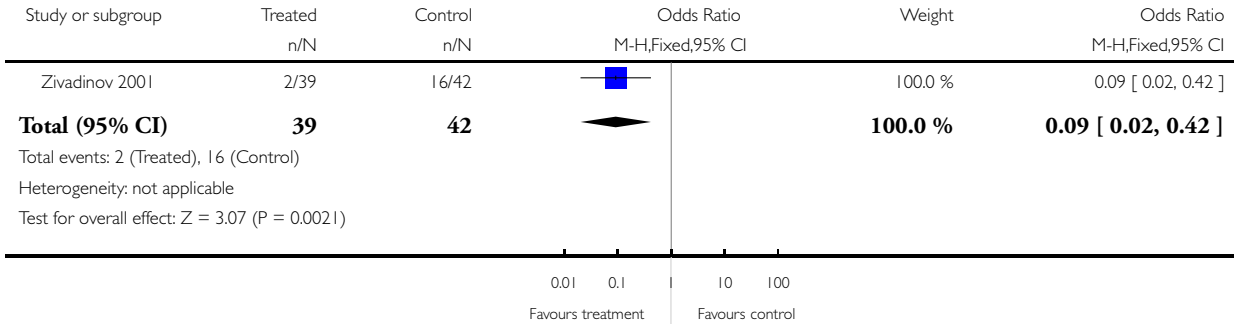


### Analysis 1.5. Comparison 1 Corticosteroids versus placebo or open control, Outcome 5 Disability progression at year 2.

Review: Corticosteroids for the long-term treatment in multiple sclerosis

Comparison: 1 Corticosteroids versus placebo or open control

Outcome: 5 Disability progression at year 2

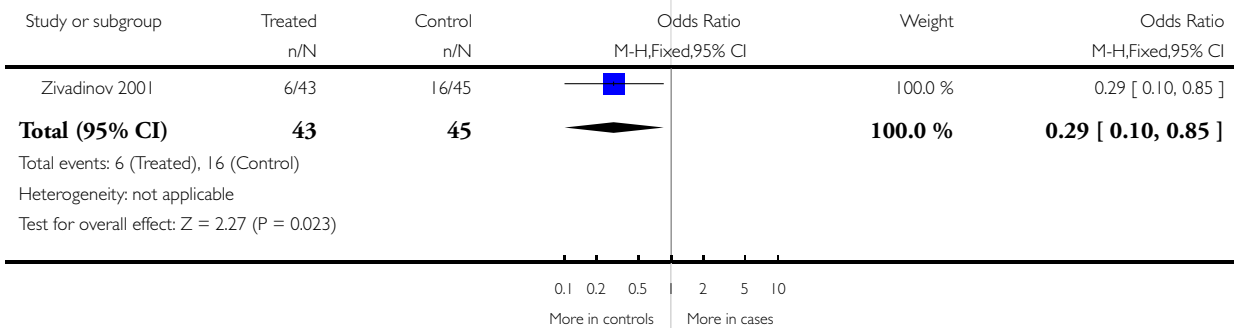


### Analysis 1.6. Comparison 1 Corticosteroids versus placebo or open control, Outcome 6 Disability progression at year 2: sensitivity analysis.

Review: Corticosteroids for the long-term treatment in multiple sclerosis

Comparison: 1 Corticosteroids versus placebo or open control

Outcome: 6 Disability progression at year 2: sensitivity analysis

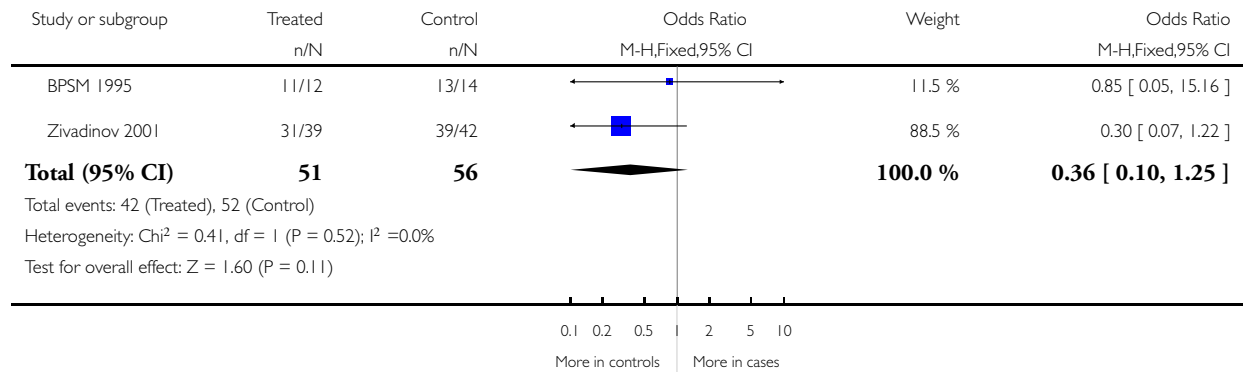


### Analysis 1.7. Comparison 1 Corticosteroids versus placebo or open control, Outcome 7 New exacerbations at end of follow-up.

Review: Corticosteroids for the long-term treatment in multiple sclerosis

Comparison: 1 Corticosteroids versus placebo or open control

Outcome: 7 New exacerbations at end of follow-up

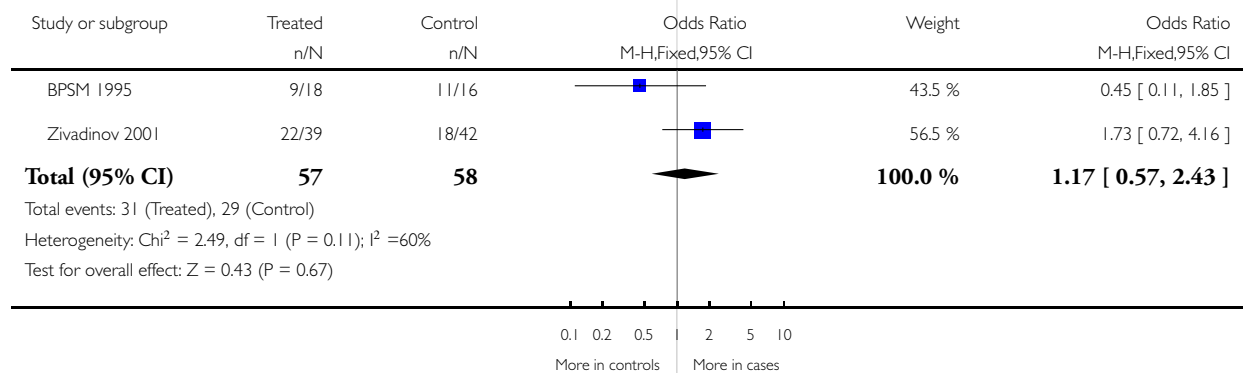


### Analysis 1.8. Comparison 1 Corticosteroids versus placebo or open control, Outcome 8 New exacerbations at year 1.

Review: Corticosteroids for the long-term treatment in multiple sclerosis

Comparison: 1 Corticosteroids versus placebo or open control

Outcome: 8 New exacerbations at year 1



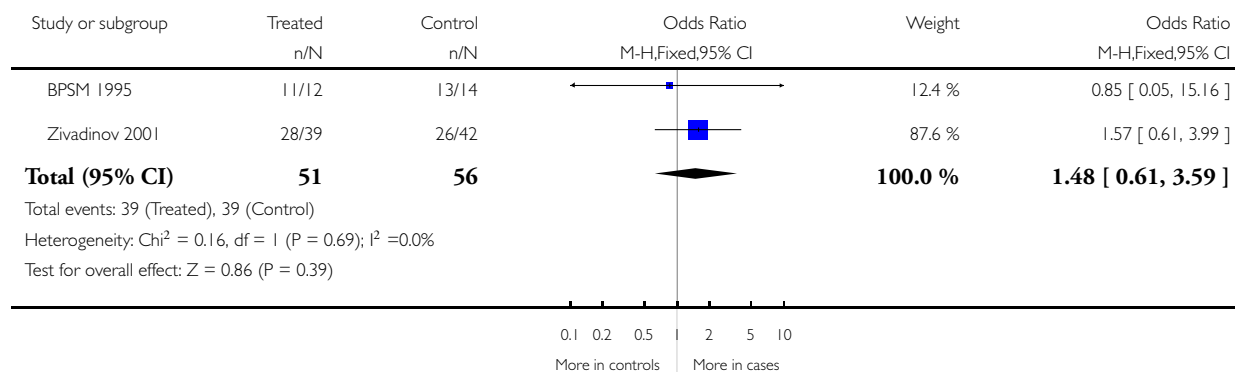


## Analysis 1.9. Comparison 1 Corticosteroids versus placebo or open control, Outcome 9 New exacerbations at year 2.

Review: Corticosteroids for the long-term treatment in multiple sclerosis

Comparison: 1 Corticosteroids versus placebo or open control

Outcome: 9 New exacerbations at year 2



## ADDITIONAL TABLES

Table 1. Form for quality assessment

Study:	Concealment	Blinding	Int-to-treat
	Concealment of randomisation	Blinding in outcome evaluation	Intention-to-treat analysis
present	YES/NO	YES/NO	YES/NO
absent	YES/NO	YES/NO	YES/NO
unclear	YES/NO	YES/NO	YES/NO

Table 2. Data Collection Form

Study	Treated N=?	Control N=?
Dropped out/excluded after randomisation	n=?	n=?
Pts who progressed* at 1 yr	n=?	n=?
Pts who progressed* at 2 yrs	n=?	n=?

**Table 2. Data Collection Form** (Continued)

Pts who progressed* at end of follow-up	n=?	n=?
Pts experiencing at least one exacerbation at 1 yr	n=?	n=?
Pts experiencing at least one exacerbation at 2 yrs	n=?	n=?
Pts experiencing at least one exacerbation at end of follow-up	n=?	n=?
Pts with severe side effects (please specify)	n=?	n=?
Other side effects (please specify)	n=?	n=?
* Progression is defined as a persistent worsening of at least one point in EDSS, recorded whilst not in relapse. Other definitions of progression could be accepted, including a persistent half-point increase starting from EDSS score 5.5		

## APPENDICES

### Appendix I. CENTRAL search strategy

#1MeSH descriptor Multiple Sclerosis explode all trees  
 #2MeSH descriptor Demyelinating Diseases, this term only  
 #3MeSH descriptor Myelitis, Transverse, this term only  
 #4MeSH descriptor Optic Neuritis explode all trees  
 #5MeSH descriptor Encephalomyelitis, Acute Disseminated, this term only  
 #6(multiple sclerosis)  
 #7(demyelinating disease\*)  
 #8(transverse myelitis)  
 #9(neuromyelitis optica)  
 #10(optic neuritis)  
 #11(encephalomyelitis acute disseminated)  
 #12(devic)  
 #13(#1 OR #1 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)  
 #14MeSH descriptor Adrenal Cortex Hormones explode all trees  
 #15MeSH descriptor Steroids explode all trees  
 #16MeSH descriptor Methylprednisolone explode all trees  
 #17MeSH descriptor Prednisolone, this term only  
 #18MeSH descriptor Dexamethasone explode all trees

#19(corticosteroids)  
 #20(steroids)  
 #21(methylprednisolone)  
 #22(prednisone)  
 #23(prednisolone)  
 #24(dexamethasone)  
 #25(acth)  
 #26MP  
 #27corticotrophic AND hormone  
 #28(#14 OR 16 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)  
 #29(#28 AND #13)

## Appendix 2. MEDLINE (PubMed) search strategy

((("Multiple Sclerosis"[mh]) OR ("Myelitis, Transverse"[mh:noexp]) OR ("Demyelinating Diseases"[mh:noexp]) OR ("Encephalomyelitis, Acute Disseminated"[mh:noexp]) OR ("Optic Neuritis"[mh])) OR (((("multiple sclerosis") OR ("neuromyelitis optica") OR ("transverse myelitis") OR (encephalomyelitis) OR (devic) OR ("optic neuritis")) OR ("demyelinating disease\*") OR ("acute disseminated encephalomyelitis")))) AND (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT ((animals[mh]) NOT ((animals[mh]) AND (human[mh]))))) AND (((corticosteroids) OR (steroids) OR (methylprednisolone) OR (MP) OR (prednisone) OR (prednisolone) OR (dexamethasone) OR (ACTH) OR (corticotrophic AND hormone)) OR (("Adrenal Cortex Hormones"[mh]) OR ("Steroids"[mh]) OR ("Methylprednisolone"[mh]) OR ("Prednisone"[mh:noexp]) OR ("Dexamethasone"[mh]) OR ("prednisolone"[mh:noexp]))))

## Appendix 3. EMBASE (EMBASE.com) search strategy

((('encephalomyelitis'/exp) OR ('demyelinating disease'/exp) OR ('multiple sclerosis'/exp) OR ('myelo optic neuropathy'/exp) OR ('multiple sclerosis':ti,ab) OR ('neuromyelitis optica':ab,ti) OR (encephalomyelitis:ab,ti) OR (devic:ti,ab)) AND (('crossover procedure'/exp) OR ('double blind procedure'/exp) OR ('single blind procedure'/exp) OR ('randomized controlled trial'/exp) OR (random\*:ab,ti) OR (factorial\*:ab,ti) OR (crossover:ab,ti) OR (cross:ab,ti AND over:ab,ti) OR (placebo:ab,ti) OR ('double blind':ab,ti) OR ('single blind':ab,ti) OR (assign\*:ab,ti) OR (allocat\*:ab,ti) OR (volunteer\*:ab,ti))) AND (('corticosteroid'/exp) OR ('steroid'/exp AND [embase]/lim) OR ('methylprednisolone'/exp) OR ('dexamethasone'/exp) OR ('corticotropin'/exp) OR (corticosteroid\*:ab,ti OR steroid\*:ab,ti OR methylprednisolone:ab,ti OR prednisolone:ab,ti OR dexamethasone:ab,ti OR corticotropin:ab,ti)) AND [humans]/lim AND [embase]/lim

## WHAT'S NEW

Last assessed as up-to-date: 2 August 2007.

Date	Event	Description
22 August 2008	Amended	Converted to new review format.

## CONTRIBUTIONS OF AUTHORS

Dr Alfonso Ciccone conceived and wrote most part of this review that was checked and discussed with the other authors who approved the final version. Dr Sandro Beretta, Dr. Fabio Brusaferrri, Dr. Ian Galea, Dr. Alessandra Protti and Dr. Chiara Spreafico selected the trials, extracted the data and assessed the quality of the trials. Dr. Fabio Brusaferrri checked all references pertinent to this review already used in two systematic reviews on corticosteroids for multiple sclerosis whose he was one of the authors. Dr. Ian Galea contacted one manufacturer of corticosteroids and active researchers known to have an interest in the use of steroids in MS in order to identify any unpublished data and wrote the “Synopsis”. Dr. Sandro Beretta shared data of an unpublished trial that was checked with Dr. Chiara Spreafico. Dr Alfonso Ciccone performed the analyses and Dr. Sandro Beretta assisted in statistical analysis. Dr. Chiara Spreafico and Dr. Alessandra Protti prepared the abstract.

## DECLARATIONS OF INTEREST

Two reviewers (Alfonso Ciccone and Sandro Beretta) had a leading role in a randomised controlled trial on pulsed high dose intravenous methylprednisolone for relapsing remitting multiple sclerosis, included in the review and quoted as [BPSM 1995](#) (Boli Steroidi Preventivi nella Sclerosi Multipla).

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Long-Term Care; Adrenal Cortex Hormones [adverse effects; \*therapeutic use]; Disease Progression; Methylprednisolone [adverse effects; therapeutic use]; Multiple Sclerosis [\*drug therapy]; Prednisolone [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic

### MeSH check words

Humans