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Corticosteroids for treating optic neuritis (Review)

Gal RL, Vedula SS, Beck R

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[Intervention Review]

Corticosteroids for treating optic neuritis

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ABSTRACT

Background

Optic neuritis is an inflammatory disease of the optic nerve. It usually presents with an abrupt loss of vision and recovery of vision is almost never complete. It occurs more commonly in women than in men. Closely linked in pathogenesis, optic neuritis may be the initial manifestation for multiple sclerosis. In some people, no underlying cause can be found.

Objectives

The objective of this review was to assess the effects of corticosteroids on visual recovery in eyes with acute optic neuritis.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2015, Issue 4), MEDLINE (January 1950 to April 2015), EMBASE (January 1980 to April 2015), Latin American and Caribbean Health Sciences Literature (LILACS) (January 1982 to April 2015), PubMed (January 1946 to April 2015), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). There were no date or language restrictions in the electronic searches for trials. The *meta*Register of Controlled Trials (*m*RCT) was last searched on 6 March 2014. The electronic databases were last searched on 7 April 2015. We also searched reference lists of identified trial reports for additional trials.

Selection criteria

We included randomized controlled trials (RCTs) that evaluated systemic corticosteroids, in any form, dose or route of administration, in people with acute optic neuritis.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included six RCTs with a total of 750 participants. Each trial was conducted in a different country: Denmark, Germany, India, Japan, UK, and United States. Additionally, we identified two ongoing trials not due to be completed until 2016. Among the six trials included in this review, we judged one to be at high risk of bias. The remaining five trials were judged to be at either low or uncertain risk of biases.

Five trials compared only two intervention groups and one trial had a three-arm comparison of oral corticosteroids or intravenous corticosteroids with placebo. Of the five trials with only two intervention groups, two trials compared oral corticosteroids versus placebo, two trials compared intravenous corticosteroids with placebo, and one trial compared intravenous dexamethasone with intravenous methylprednisolone plus oral prednisolone.

Three trials evaluating oral corticosteroids used varying doses of corticosteroids versus placebo. In the meta-analyses to assess visual acuity, the risk ratio (RR) was 1.00 (95% confidence interval (CI) 0.82 to 1.23; participants = 398) at one month; 0.92 (95% CI 0.77 to 1.11; participants = 355) at six months; and 0.93 (95% CI 0.70 to 1.24; participants = 368) at one year. In the meta-analyses of two trials evaluating corticosteroids with total dose greater than 3000 mg administered intravenously, the RR of normal visual acuity (defined as 20/20 Snellen fraction or equivalent) in the intravenous corticosteroids group compared with the placebo group was 1.05 (95% CI 0.88 to 1.26; participants = 346) at six months. The RR of contrast sensitivity in the normal range for the same comparison was 1.11 (95% CI 0.92 to 1.33; participants = 346) at six months follow-up. The RR of normal visual field for this comparison was 1.08 (95% CI 0.96 to 1.21; 346 participants) at six months; and 1.01 (95% CI 0.86 to 1.19; participants = 316) at one year. Four trials reported adverse events primarily related to gastrointestinal symptoms and sleep disturbance; one trial reported minor adverse event of acne.

Authors' conclusions

There is no conclusive evidence of benefit in terms of recovery to normal visual acuity, visual field or contrast sensitivity six months after initiation with either intravenous or oral corticosteroids at the doses evaluated in trials included in this review.

PLAIN LANGUAGE SUMMARY

Corticosteroids for treating optic neuritis

Review question
We reviewed the evidence about the effects of corticosteroids on visual recovery of people with acute optic neuritis.

Background
Optic neuritis is inflammation of the optic nerve leading to sudden loss of vision that takes place over the course of several hours or days. The optic nerve, which enters the back of the eye, carries visual information from the eye to the brain. When the optic nerve becomes inflamed, damage may occur. Thus information from the eye to the brain is interrupted, resulting in temporary or permanent vision loss. Optic neuritis is closely linked to multiple sclerosis (MS), an inflammatory disease that affects nerve cells generally. Corticosteroids have been widely used in the treatment of optic neuritis due to their anti-inflammatory effects.

Study characteristics
For this systematic review, we identified six trials conducted in Denmark, Germany, India, Japan, United Kingdom, and United States, which included 750 participants. These trials compared corticosteroid treatment with placebo or another treatment; they varied in the way corticosteroids were given and the dose. Two trials compared oral corticosteroids versus placebo; three trials compared intravenous corticosteroids versus placebo; one trial compared two types of intravenous corticosteroids; and one trial with three groups compared oral corticosteroids versus intravenous corticosteroids versus placebo. Participants in all six trials were followed up for at least three months. Outcomes of visual acuity, contrast sensitivity in the normal range and visual field were assessed at 1, 6, and 12 months. Quality of life also was assessed and reported in one trial. The information is current as of 7 April 2015.

Key results
There was no available evidence of beneficial effect from oral or intravenous corticosteroids compared with placebo for the visual acuity, visual field, and contrast sensitivity outcomes. Adverse effects, although not consistently reported, included dermatological symptoms, endocrinological disorders, gastrointestinal problems, headache, fever, sleep disturbance and psychiatric problems. Severe adverse events were reported in the intravenous steroid treatment group of one trial. The investigators of three trials concluded that minor adverse events were more common in steroid groups than in the placebo group.

Quality of the evidence
Out of six trials included in this review, we assessed one trial to have high risk of bias due to including a subset of participants who were allowed to choose their intervention. The remaining five trials were of either low or uncertain risk of biases.

BACKGROUND

Description of the condition

Optic neuritis is an inflammatory disease of the optic nerve. It is second only to glaucoma as the most common acquired optic nerve disorder in persons under 50 years. The majority of people with optic neuritis are between the ages of 20 and 50 years, with a mean age ranging from 30 to 35 years. In population-based studies in the United States, the annual incidence of optic neuritis has been estimated to be between 1 and 5 per 100,000 (Beck 1998). Koch-Henriksen and Hyllested reported an annual incidence of 4 to 5 per 100,000 for new onset optic neuritis cases in Denmark from 1948 to 1964 (Koch-Henriksen 1988). In Olmstead County, Minnesota, United States the prevalence rate of optic neuritis was estimated as 115 per 100,000 (Rodriguez 1995). Women are more often affected than men. Optic neuritis is closely linked to multiple sclerosis (MS) and in most cases has a similar pathogenesis (Lightman 1987). It may be the first manifestation of multiple sclerosis or occur later in its course (Ebers 1985). A similar, yet distinct condition to multiple sclerosis known as neuromyelitis optica, or Devic's disease, also is characterized by optic neuritis. Because neuromyelitis optica is very rare and is treated with a different course than typical cases of optic neuritis, we considered optic neuritis secondary to neuromyelitis optica to be outside the scope of this review.

The presenting symptom of optic neuritis usually is abrupt visual loss in one eye taking place over several hours or days, accompanied by mild pain. In about 10% of cases, symptoms occur in both eyes either simultaneously or sequentially (de la Cruz 2006). A clinical diagnosis of optic neuritis may be made based on the following: age between 18 and 45 years, sudden visual loss with progression within one week, pain with eye movement, absence of inflammation in the vitreous or anterior chamber, and improvement in vision that begins within three to four weeks of initial symptoms. The prognosis for visual recovery after acute optic neuritis is generally good; however, most people have some lasting visual impairment. Even when an individual's visual acuity does return to normal, abnormalities frequently remain in other measures such as contrast sensitivity, color vision, and visual field (Fleishman 1987; Sanders 1986).

Description of the intervention

Corticosteroids have been used since the early 1950s to treat acute optic neuritis because of their anti-inflammatory effects. Initially, some experts advocated treatment with oral prednisone while others recommended alternative or no treatment. In the 1980s, anecdotal reports suggested that high-dose intravenous corticosteroids might be effective (Spoor 1988). In 1992, the National Eye Institute of the United States National Institutes of Health funded a randomized controlled trial to test the efficacy of corticosteroids in the treatment of optic neuritis (ONTT 1992-2006). Based on results of this trial the current guidelines in the United States suggest either administration of high-dose intravenous methylprednisolone to hasten recovery of vision or no treatment. No other treatment has been shown to aid recovery of vision lost due to acute optic neuritis.

How the intervention might work

By controlling the inflammation associated with optic neuritis, it is believed that visual recovery may be quicker, permanent damage to the optic nerve may be prevented, or both. However, corticosteroids, along with having anti-inflammatory properties, also have known side effects such as hypertension and may lead to other eye disease such as glaucoma or cataract.

Why it is important to do this review

Prior to the Optic Neuritis Treatment Trial (ONTT) (ONTT 1992-2006), well-established guidelines for treating optic neuritis did not exist. Brusaferri and Candelise published a meta-analysis of steroids for multiple sclerosis and optic neuritis with inclusion criteria for participants and treatment type different from those specified for this review (Brusaferri 2000). A systematic review of available studies is needed to further explore the value of corticosteroids in treating optic neuritis.

We first published a Cochrane review of this topic in 2007 (Vedula 2007), for which we identified five trials of corticosteroid use in participants with acute optic neuritis compared with placebo or no treatment (Kapoor 1998; ONMRG 1999; ONTT 1992-2006; Sellebjerg 1999; Tübingen Study 1993). In an update of the review in 2012 (Gal 2012), we identified one additional trial that had investigated the effects of two corticosteroids head-to-head (Menon 2007).

OBJECTIVES

The objective of this review was to assess the effects of corticosteroids on visual recovery in eyes with acute optic neuritis.

METHODS

Criteria for considering studies for this review

Types of studies

This review included only randomized controlled trials (RCTs).

Types of participants

We included trials in which the participants had acute optic neuritis. We did not consider participants diagnosed with neuromyelitis optica, or Devic's disease, as this condition is treated differently than cases of optic neuritis due to other causes. There were no age limitations.

Types of interventions

We included trials in which systemic corticosteroid therapy was administered in any form or dosage with the intention to treat or reduce the symptoms of acute optic neuritis and compared with placebo, sham, no treatment, or types of corticosteroid administered via the same route. We excluded studies that only compared routes of administration. We did not limit inclusion of trials in this review based on the duration of treatment or the length of follow-up.

Types of outcome measures

Primary outcomes

The primary outcomes for comparison of interventions were visual outcomes measured as:

(1) Proportion of participants with normal visual acuity, defined as best-corrected 20/20 Snellen fraction or equivalent, at six months or more;
(2) Proportion of participants with contrast sensitivity in the normal range at six months or more;

(3) Proportion of participants with normal visual field, defined as greater than −3.00 dB by Goldmann perimeter test, at six months or more.

Secondary outcomes

Secondary outcomes comparison of interventions were immediate response (rate of recovery) measured as:

(1) Proportion of participants with normal visual acuity at one month;
(2) Proportion of participants with contrast sensitivity in the normal range at one month;
(3) Proportion of participants with normal visual field at one month.

We compared adverse outcomes related to treatment. We also planned to compare data on quality of life whenever available.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2015, Issue 4), MEDLINE (January 1950 to April 2015), EMBASE (January 1980 to April 2015), Latin American and Caribbean Health Sciences Literature (LILACS) (January 1982 to April 2015), PubMed (January 1946 to April 2015), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not impose any language or date restrictions in the search for trials. The *meta*Register of Controlled Trials (*m*RCT) was last searched 6 March 2014. The electronic databases were last searched on 7 April 2015.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), PubMed (Appendix 5), *m*RCT (Appendix 6), ClinicalTrials.gov (Appendix 7) and the ICTRP (Appendix 8).

Searching other resources

We searched the reference lists of identified trial reports to find additional trials and used the Science Citation Index to find studies that may have cited the identified trials. We did not conduct manual searches of conference abstracts specifically for this review.

Data collection and analysis

Selection of studies

Two review authors independently assessed the titles and abstracts of all records identified by the electronic and other searches. We retrieved full-text reports of potentially or definitely relevant trials as assessed by at least one review author and reviewed these according to the definitions in the 'Criteria for considering studies for this review'. For potentially relevant trials published in non-English languages, we translated the Methods and Results sections and then assessed the trials for inclusion. Two review authors independently categorized the reports as 'include' or 'exclude'. A third review author resolved any disagreements. We documented excluded studies and the reasons for exclusion in the 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors independently extracted data on study characteristics, such as methods, details of participants, interventions, outcomes, and other relevant information. We used paper data collection forms for duplicate data abstraction and resolved discrepancies by consensus. One review author entered data into Review Manager software (RevMan 2014); and a second review author verified all data entered. We contacted trial investigators for data that were missing or unclear in the trial reports. When investigators did not respond within six weeks or we were not able to communicate with them, we used data as available from the reports.

Assessment of risk of bias in included studies

Two review authors, unmasked to the trial lists, institutions and trial results, assessed included trials for risk of bias in several domains of potential bias according to methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A third review author resolved any disagreements. We evaluated each trial for bias in the following domains: selection bias (sequence generation and allocation concealment before randomization), performance bias (masking of participants and study personnel), detection bias (masking of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other sources of bias. We judged each trial as being at 'low', 'high', or 'unclear' risk of bias for each domain. We contacted trial investigators for additional information on issues that were unclear from information available in the trial reports. When investigators did not respond within six weeks or we were not able to communicate with them, we assigned judgment based on the information available.

Measures of treatment effect

We calculated summary risk ratios (RRs) with 95% confidence intervals (CIs) for all outcomes. RRs greater than 1 indicate the normality of the outcome (visual acuity, contrast sensitivity and visual field) is achieved more often in the corticosteroid group than the control group.

Unit of analysis issues

The unit of analysis was the individual participant for all outcomes. All trials enrolled unilateral cases of acute optic neuropathy; thus, analyses by participant are equivalent to analyses by eye.

Dealing with missing data

We contacted the primary investigators of included trials to obtain data not reported for some participants. We used available data included in the trial reports when there was no response within six weeks. We did not impute data for the purposes of this review.

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity by examining potential variations in participant characteristics, interventions compared, and assessments of primary and secondary outcomes among included trials. We used the I^2 statistic (%) to determine the proportion of variation due to statistical heterogeneity, with a value above 50% considered to represent substantial statistical heterogeneity. We also examined results of the Chi^2 test and the degree of overlap in confidence intervals of included trials to assess heterogeneity. Poor overlap of confidence

intervals on treatment effect estimates suggest heterogeneity among trials.

Assessment of reporting biases

We planned to examine funnel plots to assess possible publication bias when 10 or more trials were included in meta-analysis. We assessed for selective outcome reporting at the trial level as part of the assessment of risk of bias in included trials.

Data synthesis

When there was no important clinical or methodological heterogeneity among trials, we summarized the results of the trials in meta-analyses. We used a random-effects model in each analysis. We did not summarize results with meta-analysis when substantial statistical heterogeneity (I^2 greater than 50%) was present; instead we reported individual trial results only.

Subgroup analysis and investigation of heterogeneity

We did not conduct subgroup analyses for this review due to insufficient data. Two trials reported subgroup analyses for different outcomes (Kapoor 1998 Sellebjerg 1999). One reported visual outcomes separately for long and short lesions (Kapoor 1998); the other reported a post hoc subgroup analysis and concluded that participants with a more severe baseline visual deficit had more pronounced response to high-dose methylprednisolone treatment. Therefore, we only documented the results from these trials. If sufficient and comparable data are reported in future updates to this review, we will conduct subgroup analyses.

Sensitivity analysis

We did not conduct planned sensitivity analyses to determine the impact of exclusion of trials with high risk of bias, exclusion of unpublished trials, and exclusion of industry-funded trials because of the lack of a sufficient number of trials in these categories.

RESULTS

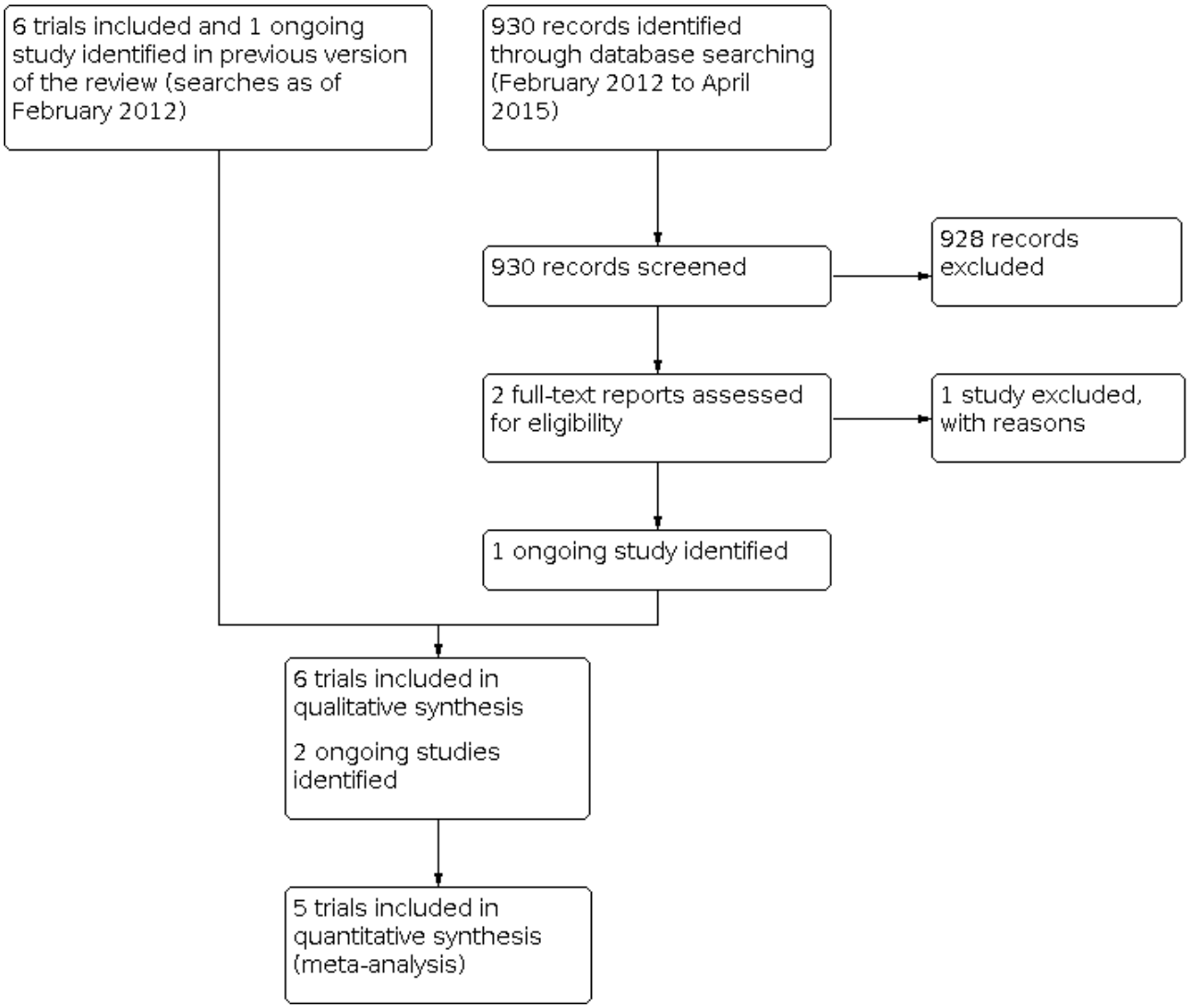
Description of studies

Results of the search

The electronic searches for the previous published versions of this review were conducted in January 2006 and February 2012 and yielded 430 and 815 records, respectively. As of February 2012, we had included six trials in the review (Kapoor 1998; Menon 2007; ONMRG 1999; ONTT 1992-2006; Sellebjerg 1999; Tübingen Study 1993); and identified one ongoing trial (NCT01524250).

In the most recent electronic searches performed on 7 April 2015, we identified 873 additional titles and abstracts along with 57 records in trial registers (Figure 1). We retrieved and excluded the full-text report of one potentially relevant study (Al-Eajailat 2014); and identified one ongoing trial (NCT01838174). We identified no new trials for inclusion in this updated review.

Figure 1. Study flow diagram.



Included studies

We included six trials in which a total of 750 participants had been randomized. Detailed characteristics of the individual trials are presented in the 'Characteristics of included studies' table.

Types of participants

Four trials restricted participants to those with no history of prior attacks of optic neuritis in the affected eye (Kapoor 1998; ONTT 1992-2006; Menon 2007; Tübingen Study 1993). Kapoor 1998 included only participants with confirmed multiple sclerosis, while the remaining trials included people with optic neuritis of unknown or demyelinating etiologies. ONMRG 1999 enrolled only participants with acute symptoms of unilateral optic neuritis of unknown or demyelinating origin, with relative afferent pupillary defect and a normal or swollen optic disc in the affected eye. Sellebjerg 1999 included participants with optic neuritis and visual acuity of 0.7 or less (Snellen decimal fraction) in the affected eye.

All trials restricted participants to those with a short period since onset of visual symptoms. Participants had visual symptoms for less than two weeks in ONMRG 1999; less than eight days in ONTT 1992-2006 and Menon 2007; less than three weeks in Tübingen Study 1993; and less than four weeks in Kapoor 1998 and Sellebjerg 1999. Participants with a history of treatment with corticosteroids were excluded from five trials (Menon 2007 ONMRG 1999 ONTT 1992-2006 Sellebjerg 1999 Tübingen Study 1993).

Types of interventions

The six trials had various comparisons. Five trials compared only two intervention groups; whereas ONTT 1992-2006 was a three-arm trial comparing oral corticosteroids or intravenous corticosteroids with placebo. In all, three trials compared oral corticosteroids versus placebo (ONTT 1992-2006; Sellebjerg 1999; Tübingen Study 1993), three trials compared intravenous corticosteroids with placebo (Kapoor 1998; ONMRG 1999; ONTT 1992-2006), and one trial compared intravenous dexamethasone with intravenous methylprednisolone plus oral prednisolone (Menon 2007).

The description of doses of corticosteroids evaluated in each of the trials in the text of this review refers to the total dose administered over the specified treatment period. The treatment

regimens of the individual trials are described in greater detail in the 'Characteristics of included studies' table. The total dose of corticosteroid administered to participants in the treatment arms in the included trials varied from 200 mg in Menon 2007 to more than 3770 mg in the intravenous corticosteroid arm of the ONTT 1992-2006. The control intervention was intravenous mecobalamin (B12) in ONMRG 1999; and oral thiamine (B1) in Tübingen Study 1993. Because of systemic treatment administration in all included trials, randomization was by participant.

Types of outcomes

Investigators of all trials measured and reported visual acuity as an outcome. Contrast sensitivity was reported from five trials (Kapoor 1998; Menon 2007; ONMRG 1999; ONTT 1992-2006; Sellebjerg 1999). In all trials, visual field was measured; Sellebjerg 1999 did not assess visual field in a systematic manner (personal communication with Dr. Sellebjerg). In four trials, personnel assessed color vision (Menon 2007; ONMRG 1999; ONTT 1992-2006; Sellebjerg 1999). Menon 2007 also reported stereoacuity and visual evoked response as outcomes. Only ONTT 1992-2006 reported quality of life as an outcome, but assessments were made at 5 to 18 years after trial entry.

There was variability in the method employed to assess different outcomes as noted in the 'Characteristics of included studies' table. Menon 2007 presented mean values for visual acuity, visual field (data not shown in report), and contrast sensitivity instead of defining normal values for each. Normal visual acuity was defined as 20/20 Snellen fraction or equivalent in the other five included trials, normal visual field was defined as greater than −3.00 dB by Goldmann perimeter test; contrast sensitivity was measured in various ways. Normal contrast sensitivity was defined as greater than 1.65 log units in ONTT 1992-2006 and ONMRG 1999. Sellebjerg 1999 measured contrast sensitivity using Arden gratings and defined normal as less than or equal to 80 points. Kapoor 1998 considered normal contrast sensitivity to be greater than 1.35 dB by Humphrey automated perimetry when carried out using the manufacturer's 30-2 protocol.

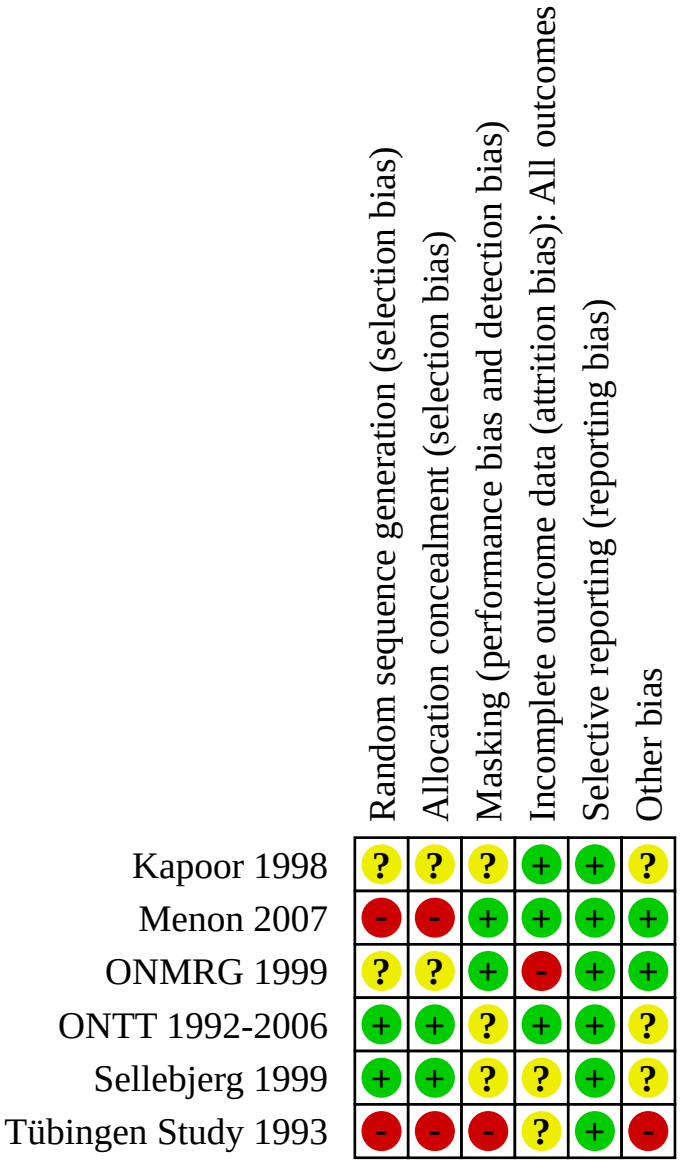
Excluded studies

We excluded 21 studies, listed in the 'Characteristics of excluded studies' table with reasons for exclusion.

Risk of bias in included studies

Figure 2 presents a summary of the 'Risk of bias' assessments for the included trials. For nearly half the total number of domains we could not assess risk of bias from available information and designated the risk of bias to be 'unclear'. Descriptions of our judgments and classifications for each domain are summarized below.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All trials were reported as randomized, but only two reported adequate methods of sequence generation and allocation concealment before randomization (ONTT 1992-2006; Sellebjerg 1999). We judged two trials at high risk of selection bias: Menon 2007 reported that participants were randomized by block randomization, yet in correspondence with the author, the author clarified that the first case was decided by a toss of a coin and all subsequent assignments were decided by alternate assignment; and Tübingen Study 1993 reported a subgroup of participants who chose their own treatment, and therefore the sequence for the treatment assignments was not properly generated and the allocations were not concealed for this subgroup. We deemed the remaining two trials as having had unclear risk of selection bias due to inadequate reporting of information (Kapoor 1998; ONMRG 1999).

Masking (performance bias and detection bias)

We assessed two trials at low risk of performance bias and detection bias as participants, personnel, and outcome assessors were masked (Menon 2007; ONMRG 1999). We judged three trials at unclear risk of bias: only two of the three treatment groups were masked in ONTT 1992-2006 and two trials were reported as 'double-blind' but did not provide procedural details (Kapoor 1998;

Sellebjerg 1999). In one trial, a group of participants (12 of 50) declined to be randomized and masked, thus we judged this trial to be at high risk of performance and detection bias (Tübingen Study 1993).

Incomplete outcome data

We judged three trials at low risk of attrition bias for low (less than 5%) or no loss to follow-up through six months (Kapoor 1998; Menon 2007; ONTT 1992-2006). We judged one trial, in which only a portion of participants could be assessed for some outcomes at each follow-up time point, as at high risk of attrition bias (ONMRG 1999). We judged Sellebjerg 1999 and Tübingen Study 1993 at unclear risk of attrition bias because there was missing data for more than 10% of participants and participants with protocol violations, poor compliance, or both were excluded from analysis by trial investigators.

Selective reporting

We judged all six trials at low risk of selective reporting bias because the investigators reported pre-specified primary and secondary outcomes of interest (ONTT 1992-2006; Sellebjerg 1999); or reported outcomes based on outcomes described in the trial reports (Kapoor 1998; Menon 2007; ONMRG 1999; Tübingen Study 1993).

Other potential sources of bias

We judged three trials to have unclear risk of other bias because they reported receiving funding or study medication from the pharmaceutical companies (ONTT 1992-2006; Sellebjerg 1999); or modified analysis by pooling treatment and control groups (Kapoor 1998). We judged one trial to be at high risk of other potential bias due to the funding from pharmaceutical industry and because a subgroup of participants chose the assignment by their own decision (Tübingen Study 1993). We considered the remaining trials as having had low risk of other potential sources of bias (Menon 2007; ONMRG 1999).

Effects of interventions

We did not combine all included trials in a single meta-analysis because the doses and routes of administration of corticosteroids differed among trials, constituting clinical heterogeneity of interventions. Three trials compared oral administration of corticosteroids with no corticosteroids. Oral corticosteroid doses ranged from 1 mg to 500 mg per day with tapered doses up to 5 mg; the treatment periods were 10 days in Sellebjerg 1999, 18 days in ONTT 1992-2006, and 21 days in Tübingen Study 1993. Three trials compared intravenous administration of corticosteroids with no corticosteroids. Intravenous corticosteroid doses ranged from 1 mg to 1000 mg per day for up to 3 days (Kapoor 1998; ONMRG 1999; ONTT 1992-2006). One trial compared intravenous dexamethasone versus intravenous methylprednisolone followed by oral prednisone for 3 days (Menon 2007).

Oral corticosteroids versus placebo

Three included trials provided data for this comparison (ONTT 1992-2006; Sellebjerg 1999; Tübingen Study 1993).

Visual acuity

At one month, data were available from ONTT 1992-2006, Sellebjerg 1999 and Tübingen Study 1993, and the pooled risk ratio of normal visual acuity was 1.00 (95% CI 0.82 to 1.23; participants = 398). At 6 months, in a meta-analysis of ONTT 1992-2006 and Tübingen Study 1993, the risk ratio of normal visual acuity was 0.92 (95% CI 0.77 to 1.11; participants = 355). At one year, data on normal visual acuity were available from ONTT 1992-2006, Tübingen Study 1993 and Sellebjerg 1999, and the risk ratio was 0.93 (95% CI 0.70 to 1.24; participants = 368) (Analysis 1.1). The risk ratio for normal visual acuity at 6 months was 0.93 (95% CI 0.76 to 1.13) in ONTT 1992-2006; and 0.89 (95% CI 0.55 to 1.42) in Tübingen Study 1993. The risk ratio for normal visual acuity at one year in ONTT 1992-2006 was 0.76 and favored placebo (95% CI 0.63 to 0.92). The risk ratio for normal visual acuity at one year was 1.09 (95% CI 0.82 to 1.44) in Tübingen Study 1993, and 1.10 (95% CI 0.67 to 1.80) in Sellebjerg 1999; unlike ONTT 1992-2006, there was no important difference between outcomes by trial arms.

Contrast sensitivity

At one month, the risk ratio of contrast sensitivity in the normal range was 1.00 (95% CI 0.90 to 1.12) in ONTT 1992-2006; and 1.16 (95% CI 0.40 to 3.39) in Sellebjerg 1999. At six months, ONTT 1992-2006 was the only trial that reported contrast sensitivity. Among 156 participants in oral corticosteroids group, 87 had contrast sensitivity in normal range, among 150 participants in placebo group, 82 of whom had contrast sensitivity in normal range (RR 1.05; 95% CI 0.67 to 1.64). At one year, the risk ratio for contrast sensitivity in the normal range was 0.93 (95% CI 0.86 to 1.00) in ONTT 1992-2006 and 1.58 (95% CI 0.64 to 3.85) in Sellebjerg 1999 (Analysis 1.2).

Visual field

Visual field data were reported from only two trials (ONTT 1992-2006; Tübingen Study 1993). The risk ratio for normal visual field at six months was 1.00 (95% CI 0.87 to 1.14) in ONTT 1992-2006 and 1.05 (95% CI 0.87 to 1.27) in Tübingen Study 1993. Comparison of visual field outcomes at one month and one year similarly showed no benefit to oral corticosteroids from ONTT 1992-2006 and Tübingen Study 1993. At one month, the risk ratio for normal visual field was 1.16 (95% CI 0.88 to 1.51) in ONTT 1992-2006 and 1.51 (95% CI 0.92 to 2.49) in Tübingen Study 1993. At one year, the risk ratio for normal visual field was 0.94 (95% CI 0.79 to 1.12) in ONTT 1992-2006 and 0.99 (95% CI 0.83 to1.17) in Tübingen Study 1993 (Analysis 1.3).

Adverse effects

Adverse effects were reported in three included trials (ONTT 1992-2006; Sellebjerg 1999; Tübingen Study 1993). Sellebjerg 1999 reported no serious adverse effects and Tübingen Study 1993 reported only acne. The ONTT 1992-2006 reported depression, acute pancreatitis, weight gain, sleep disturbance, mild mood change, stomach upset, and facial flushing. The proportion of participants experiencing adverse effects of corticosteroid therapy was not consistently reported by all trials, thereby precluding any comparison.

Quality of life outcomes

Quality of life was assessed and reported only in ONTT 1992-2006 using participant-reported responses to the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) several years after the initial acute optic neuritis event (Mangione 1998). However, no comparative quality of life data by assigned treatment arm were available.

Intravenous corticosteroids (total dose ≥ 3000 mg) versus placebo

Three included trials provided data for comparison of outcomes (Kapoor 1998; ONMRG 1999; ONTT 1992-2006).

Visual acuity

Only one study reported data for visual acuity at one month (ONTT 1992-2006). In ONTT 1992-2006, 87 of 144 participants in corticosteroid group and 79 of 141 participants in placebo group reported having normal visual acuity at one month (RR 1.08; 95% CI 0.89 to 1.31). In a meta-analysis of Kapoor 1998 and ONTT 1992-2006 for evaluating corticosteroid of dose greater than 3000 mg administered intravenously versus placebo, the risk ratio of normal visual acuity at six months follow-up was 1.05 (95% CI 0.88 to 1.26; participants = 346) (Analysis 2.1). At one year follow-up, two trials reported visual acuity but used different scales; meta-analysis was not conducted. In ONTT 1992-2006, 105 of 137 participants in corticosteroid group versus 96 of 133 in the placebo group had normal visual acuity using a retro-illuminated ETDRS chart (RR 1.27; 95% CI 0.73 to 2.19). In ONMRG 1999, visual acuity better than Snellen decimal fraction of 1.0 (20/20) was noted in 25 of 33 participants in the corticosteroid group and 23 of 33 participants in the control group (RR 1.36; 95% CI 0.46 to 4.04).

Contrast sensitivity

At one month, data on contrast sensitivity in the normal range were available from ONMRG 1999 and ONTT 1992-2006, with risk ratio of 1.85 (95% CI 0.93 to 3.66) reported in ONMRG 1999; and 1.06 (95% CI 0.95 to 1.17) reported in ONTT 1992-2006 (Analysis 2.2). In a meta-analysis of Kapoor 1998 and ONTT 1992-2006, the risk ratio of contrast sensitivity in the normal range was 1.11 (95% CI 0.92 to 1.33; participants = 346) at six months follow-up (Analysis 2.3). At one year, data on contrast sensitivity in the normal range were available from ONMRG 1999 and ONTT 1992-2006. The risk ratio of contrast sensitivity in the normal range at one year follow-up was 1.33 (95% CI 1.02 to 1.72) in ONMRG 1999; and 0.99 (95% CI 0.93 to 1.06) in ONTT 1992-2006 (Analysis 2.4).

We have not reported a meta-analysis for this outcome at one year because there was substantial statistical heterogeneity (I^2 = 79%; P value for the Chi^2 test of homogeneity = 0.01). Similarly, we found substantial heterogeneity among estimates of this outcome at one month with data from ONMRG 1999 and ONTT 1992-2006 (I^2 = 63% and P value for Chi^2 test of homogeneity = 0.10). Though the P value for the Chi^2 test was greater than 0.05, the test has low power when used with few studies.

Visual field

One-month data were available from ONMRG 1999 and ONTT 1992-2006 with the pooled risk ratio of normal visual field equaling 1.56, but it is not statistically significant (95% CI 0.88 to 2.76; participants = 330; I^2 = 33% and P value for Chi^2 test = 0.22) (Analysis 2.5). Six-month visual field data were available from Kapoor 1998 and ONTT 1992-2006. The pooled risk ratio of normal visual field at six months follow-up was 1.08 (95% CI 0.96 to 1.21; participants = 346) (Analysis 2.6). One-year data were available from ONMRG 1999 and ONTT 1992-2006. At one year the pooled risk ratio of normal visual field was 1.01 (95% CI 0.86 to 1.19; participants = 316) (Analysis 2.7).

Adverse events

Adverse events were not reported in Kapoor 1998. In ONMRG 1999, hyperglycemia was noted in four participants; constipation, diarrhea, acneiform eruption and hyperlipidemia were reported for two participants; headache and increasing fever were reported for one participant, and transient diarrhea was reported by two participants. In ONTT 1992-2006, acute transient depression developed in one participant and acute pancreatitis was diagnosed in another participant in the intravenous-methylprednisolone group; sleep disturbance, mild mood change, stomach upset, facial flushing, and weight gain were reported for participants in both groups.

Quality of life outcome

Quality of life was assessed and reported only in ONTT 1992-2006 using participant-reported responses to the National Eye Institute Visual Functioning Questionnaire (NEI-VFQ) several years after the initial acute optic neuritis event (Mangione 1998). However, no comparative quality of life data by assigned treatment arm were available.

Intravenous dexamethasone versus intravenous methylprednisolone followed by oral prednisone

Only one trial provided data for this comparison (Menon 2007).

Visual acuity

In Menon 2007, investigators reported LogMAR mean values for visual acuity for both treatment arms. At one month follow-up, the mean ± SD was 0.42 ± 0.42 in the methylprednisolone group compared to 0.29 ± 0.29 in the dexamethasone group. At three months of follow-up the mean ± SD was 0.36 ± 0.41 in the methylprednisolone group and 0.28 ± 0.33 in the dexamethasone groups respectively. The difference was not statistically significant but favored methylprednisolone group.

Contrast sensitivity

At one month of follow-up, mean ± SD contrast sensitivities (by Pelli-Robson chart) were 1.16 ± 0.48 and 1.25 ± 0.43 in the methylprednisolone and dexamethasone treatment groups respectively in Menon 2007. At three month follow-up, the mean ± SD was 1.26 ± 0.41 in the methylprednisolone group and 1.37 ± 0.29 in the dexamethasone group, showed the significant improvement during the follow-up subsequent to the treatments.

Visual field

Limited data were available from Menon 2007 regarding visual field outcomes. Of the two participants in the methylprednisolone group who provided data on visual fields, both had a central scotoma observed in the pretreatment visual field assessment. Following treatment, at three-month follow-up the central scotoma had not resolved fully in one participant. Four participants were determined to have a central scotoma among the six participants in the dexamethasone group who underwent the pretreatment visual field assessment. The central field of the eyes of two participants failed to fully recover at three months follow-up.

Adverse events

In Menon 2007, six participants were reported to have experienced generalized weakness, one participant had sleep disturbance and

weight gain, two participants experienced depression and five participants suffered gastric irritation.

Quality of life outcomes

Quality of life was not assessed and reported in Menon 2007.

DISCUSSION

Summary of main results

Acute demyelinating optic neuritis is a common form of optic neuritis, with inflammation of the optic nerve that often is associated with multiple sclerosis. Optic neuritis is the initial manifestation of multiple sclerosis in some people (Kurtzke 1985). In this systematic review performed to evaluate the effects of corticosteroid therapy in participants with optic neuritis, we included six randomized controlled trials. We did not conduct a meta-analysis including all trials because of clinical heterogeneity resulting from variations in doses and routes of administration of corticosteroids. However, we conducted a meta-analysis of trials evaluating similar doses of corticosteroids (3000 mg or more) administered by the oral route and the intravenous route. The ONTT was the largest of the included trials and contributed the most weight in all the meta-analyses, which used the inverse weighting approach (ONTT 1992-2006). While none of the other included trials reported an evidence of benefit with intravenous corticosteroids, the results of our analyses are consistent with the effects on vision of intravenous corticosteroids reported by the ONTT investigators (ONTT 1992-2006). The 95% confidence intervals for the pooled risk ratios of normal visual acuity, contrast sensitivity in the normal range, and normal visual field at six months for the oral corticosteroids arm and the intravenous route in ONTT include the null value, thus suggesting no evidence of benefit with either oral or intravenous corticosteroids compared to placebo in this large trial for the outcomes of interest in this review (ONTT 1992-2006). This observation is consistent with the analyses of ONTT outcome data when adjusted for baseline visual acuity (ONTT 1992-2006). A life-table analysis reported in the same article indicated that the rate of return of vision to normal was higher with intravenous corticosteroids than with placebo (P = 0.09 for visual acuity, 0.02 for contrast sensitivity and 0.0001 for visual field). No statistically significant difference was found for the same outcomes for oral corticosteroids compared with placebo in a life-table analysis in the trial report. However, ONTT participants treated with oral corticosteroids had a higher rate of new episodes of optic neuritis compared with those in the placebo arm. The pooled risk ratio indicated a statistically significant benefit with respect to achieving a normal visual field at one month for participants treated with intravenous corticosteroids.

Finally, there was no evidence of benefit when intravenous corticosteroids were compared to intravenous followed by oral corticosteroids for the visual acuity and contrast sensitivity outcomes (Menon 2007).

Overall completeness and applicability of evidence

The trials evaluating oral corticosteroids were very heterogeneous in dose of medication, method of corticosteroid delivery, and comparison group. For the comparisons where meta-analysis was possible, there was no evidence of benefit with oral or intravenous corticosteroids for each of the outcomes considered. The 95% confidence intervals for the risk ratio of normal visual acuity, contrast sensitivity and visual field included the null value. Oral corticosteroids, however, resulted in statistically significantly fewer ONTT participants who had achieved normal visual acuity by one year compared with the placebo group and was consistent with our review findings. Our review has included no comparison of outcomes between higher and lower doses of corticosteroids. Adverse effects were inconsistently reported; comparisons of different management strategies were not possible. Therefore, the effectiveness and safety of corticosteroids in treating optic neuritis was not supported by the currently available evidence.

Quality of the evidence

Based on the assessment of trial quality per pre-specified criteria, we judged the overall quality of evidence as low to moderate. Random sequence generation and allocation concealment before randomization were implemented in only two of the six included trials. Masking of participants, personnel, and outcome assessors was achieved in only two trials. Complete or nearly complete outcome data were reported from four trials. Only one trial was considered to be at high risk of selective outcome reporting bias. In addition, one trial was judged to have high risk of bias because a subgroup of participants was allowed to select their treatment; four trials were judged to be unclear risk of other bias due to source of funding to conduct the trial.

Potential biases in the review process

We are unaware of any potential biases in the review process. We searched multiple databases to identify six RCTs relevant to this review. Data extracted from the trials focused on clinical and functional outcomes and were confirmed by at least two authors. Thus, the findings regarding the effectiveness of corticosteroids on treating optic neuritis is based on established, reproducible methods. Inadequate reporting of adverse events may have led to underestimation of such outcomes.

Agreements and disagreements with other studies or reviews

Since the Optic Neuritis Treatment Trial (ONTT) was the first major study to examine corticosteroid treatment for optic neuritis, most other review articles also use data from the ONTT as the basis for their conclusions (ONTT 1992-2006). In a narrative review article by Bennett 2014, authors came to the same conclusions as this review: that short-term benefits were seen in the methylprednisolone arm of ONTT, but by one year, there was no clinically or statistically significant difference between treated and untreated participants. Another review on optic neuritis diagnosis and treatment explained corticosteroid treatment in much the same manner, reporting that treatment with corticosteroids hastens recovery but does not affect the final outcome (Toosy 2014). Brusaferri and Candelise published a meta-analysis of steroids for multiple sclerosis and optic neuritis and although the inclusion criteria and treatment type differed from this review, the conclusions were the same (corticosteroid treatment improved visual acuity at 30 days but the improvement did not differ between treatment arms to a statistically significant degree during longer follow-up) (Brusaferri 2000).

AUTHORS' CONCLUSIONS

Implications for practice

There was no conclusive treatment benefit with return to normal visual acuity, visual field or contrast sensitivity with either intravenous or oral corticosteroids at the doses evaluated by trials included in this review. Either no treatment or treatment with intravenous corticosteroid therapy followed by oral corticosteroids is appropriate; intravenous corticosteroids may benefit the patient in terms of faster recovery to normal vision. As suggested by analyses reported in the ONTT, oral corticosteroid therapy has been associated with an increase in rate of new episodes of optic neuritis (ONTT 1992-2006).

Implications for research

Among participant cohorts evaluated as part of this review, there was no conclusive treatment benefit with return to normal visual function measures within one year as the outcome of interest. Future research efforts could focus on the identification of participant subgroups who are predisposed to have permanent visual deficits and would benefit from therapy that could reduce neural damage.

The trial database included a total number of 750 participants enrolled in the six trials. Except for the ONTT, individual trials likely did not have adequate power to detect or rule out a statistically significant difference in one-year outcomes that favored corticosteroids; larger trials with longer follow-up may yield different results. Future trials evaluating the role of high dose oral corticosteroids (greater than 3000 mg) as a treatment option for optic neuritis may be warranted.

Neurological outcomes were not the focus of this review but future research to evaluate the role of high-dose oral corticosteroids as a treatment option for optic neuritis, and including the observation of neurological outcomes, may be warranted.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Kapoor 1998

Study characteristics	
Methods	**Study design:** parallel group randomized controlled trial

Kapoor 1998 *(Continued)*

	Number randomized: 66 total participants; number per group not reported **Exclusions after randomization:** none reported **Losses to follow up:** 2 at last follow-up (26 weeks) **Number analyzed:** 64; 33 in steroid group and 31 in placebo group **Unit of analysis:** participant **How were missing data handled?:** excluded from the analyses **Power calculation:** none reported
Participants	**Country:** United Kingdom **Age:** mean 32 years **Gender:** 17/66 (25.8%) men and 49/66 (74.2%) women **Inclusion criteria:** unilateral acute optic neuritis; corrected visual acuity in the affected eye of 6/9 or worse within 30 days of symptoms; patients with multiple sclerosis but without prior history of optic neuritis **Exclusion criteria:** evidence of improved vision at the time of study entry; bilateral involvement; previous ocular pathology; previous episodes of optic neuritis; psychosis; significant systemic disease including active infection, diabetes mellitus, systemic hypertension; history of tuberculosis; other contraindications to steroid treatment such as active peptic ulceration **Equivalence of baseline characteristics:** not reported
Interventions	**Intervention 1:** intravenous methylprednisolone (1 gram/day given as a single bolus) **Intervention 2:** intravenous saline **Length of follow-up:** 26 weeks
Outcomes	**Primary outcomes, as specified:** (1) Visual acuity at 26 weeks; (2) Contrast sensitivity at 26 weeks (measured using circular patches of luminance modulated vertical sine wave gratings); (3) Visual field at 26 weeks or more (Humphrey automatic perimetry using 30-2 protocol) **Secondary outcomes:** not reported **Adverse events reported:** not reported **Intervals at which outcomes were assessed:** visual acuity assessed at weeks 1, 2, 4, 8, 13, and 26, and visual function measured at 26 weeks
Notes	**Study period:** March 1991 to June 1994 **Funding sources:** supported by the Multiple Sclerosis Society of Great Britain and Northern Ireland and by the Scarfe Trust **Declarations of interest:** not reported **Reported subgroup analyses:** yes; long-lesion and short-lesion subgroups were analyzed by the trial investigators separately to assess effects of treatment on visual outcome

Risk of bias

Bias	Authors' judgement	Support for judgement

Kapoor 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment before randomization not reported.
Masking (performance bias and detection bias)	Unclear risk	"Patients in either subgroup were randomized double blind to receive IV saline or IVMP"; masking of study personnel and outcome assessors not reported otherwise.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Sixty-four of 66 patients completed 6 months clinical follow-up (33 treated, 31 placebo)"; "The MRI was repeated after 6 months in 61 of 66 patients"; "VEPs were repeated after 6 months in 43 of 66 cases".
Selective reporting (reporting bias)	Low risk	Outcomes reported as described in the methods section, though we did not have access to the original trial protocol.
Other bias	Unclear risk	"Because treatment did not appear to influence outcome, some of the results obtained in the treated and placebo groups were analyzed together".

Menon 2007

Study characteristics	
Methods	**Study design:** parallel group randomized controlled trial **Number randomized:** 21 total participants: 11 in dexamethasone group and 10 in methylprednisolone group **Exclusions after randomization:** none reported **Losses to follow up:** none reported **Number analyzed:** 21: 11 in dexamethasone group and 10 in methylprednisolone group **Unit of analysis:** participant **Power calculation:** none reported
Participants	**Country:** India **Age:** mean 29 years (range 7 to 53 years) **Gender:** 12/21 (57.1%) men and 9/21 (42.9%) women **Inclusion criteria:** previously untreated acute optic neuritis within 8 days of onset; visual acuity worse than 20/60 in affected eye **Exclusion criteria:** known systemic disease other than multiple sclerosis; history of optic neuritis attacks; prior diagnosis of multiple sclerosis treated with corticosteroids; evidence of optic disc pallor in affected eye; pre-existing ocular abnormalities that affect assessment of visual function **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** intravenous dexamethasone 200 mg (in 150 ml 5% dextrose solution) given over 1.5 to 2 hours once a day for 3 days

Menon 2007 *(Continued)*

	Intervention 2: intravenous methylprednisolone 250 mg/six-hourly (in 150 ml 5% dextrose solution) given over 1.5 to 2 hours once a day for 3 days followed by oral prednisolone for 11 days **Length of follow-up:** 90 days
Outcomes	**Primary and secondary outcomes were not differentiated** **Outcomes as reported:** (1) Visual acuity (ETDRS at 4 meters distance and Snellen at 6 meters distance) (2) Visual field (Goldmann perimeter) (3) Contrast sensitivity (Pelli-Robson chart at 1 meter) (4) Color vision (Ishihara pseudoisochromatic color vision plates) (5) Stereoacuity (Randot stereoacuity test, Wirt circle) (6) Visually evoked response (Lace electronica EREV m99 machine at 33 centimeters) (7) Other: hemogram, fasting blood glucose, immunohistocytological analysis for toxoplasmosis, chest X-ray, X-ray paranasal sinuses, aerobic and anaerobic blood cultures, orbital ultrasound and neuroimaging for cases not showing any improvement with standard therapy in either group **Adverse events reported:** generalized weakness, sleep disturbance and weight gain, depression and gastric irritation **Intervals at which outcomes were assessed:** 3 days, 1 week, 1 month, and 90 days
Notes	**Study period:** not reported **Funding sources:** not reported **Declarations of interest:** not reported **Reported subgroup analyses:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	According to the published report: "The patients were randomized into two groups by block randomization; however, in correspondence with the author "The first case was decided by a toss of a coin. All subsequent were by rotation of patients (patients were alternatively assigned to group 1 and group 2)."
Allocation concealment (selection bias)	High risk	Method of allocation concealment before randomization not reported, but could not have been concealed very long once the first few assignments had been made.
Masking (performance bias and detection bias)	Low risk	Both participants and outcome assessors were masked (blinded) to the treatment assignment (author correspondence).
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported as described in the methods section, though we did not have access to the original trial protocol.
Other bias	Low risk	None observed.

ONMRG 1999

Study characteristics	
Methods	**Study design:** parallel group randomized controlled trial **Number randomized:** 102 total participants; number per group not reported **Exclusions after randomization:** exclusions per group not explicitly stated 32 dismissed after start of trial due to different reasons including misdiagnosis and lost data; 2 participants excluded before treatment; 2 participants excluded during treatment due to withdrawal of consent by the participants **Losses to follow up:** none reported **Number analyzed (total and per group):** 66: corticosteroids group: 33; control group: 33 **Unit of analysis:** participant **Power calculation:** none reported
Participants	**Country:** Japan **Age:** 14 to 58 (mean 36.3 years) **Gender:** 22/66 (33.3%) men and 44/66 (66.7%) women **Inclusion criteria:** "The criteria for eligibility were the same as specified previously." Acute symptoms indicative of unilateral optic neuritis of unknown or demyelinating origin; visual symptoms of 14-day duration or less; relative afferent pupillary defect in affected eye; normal or swollen optic disc of affected eye **Exclusion criteria:** not reported **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** intravenous methylprednisolone (1 gram/day) for 3 days followed by oral corticosteroid for 7 to 10 days. Intravenous administration was carried out over 45 to 60 minutes once a day in the morning **Intervention 2:** intravenous mecobalamin (a control drug) (500 microgram/day) for 3 days, followed by oral mecobalamin for at least 7 days. Intravenous administration was carried out over 45 to 60 minutes once a day in the morning **Length of follow-up:** 1 year
Outcomes	**Primary and secondary outcomes were not differentiated** **Outcomes as reported:** (1) Visual acuity: measured using Landolt rings at 5 meters after full refractive correction. Results expressed as decimal acuity, measured before and at 1, 3, 4, 12 weeks and 1 year after the initiation of treatment (2) Visual field: Humphrey 30-2 for central 30 degrees of visual field and Goldmann perimetry for peripheral field if HFA unsuitable, measured before and at 1, 3, 4, 12 weeks and 1 year after the initiation of treatment (3) Color vision: measured before and at 1, 3, 4, 12 weeks and 1 year after the initiation of treatment

ONMRG 1999 *(Continued)*

	(4) Contrast sensitivity: Visual Contrast Test System at a testing distance of 1 meter, measured before and at 1, 3, 4, 12 weeks and 1 year after the initiation of treatment (5) Others: central critical flicker fusion frequency tested before and at 1, 3, 4, 12 weeks and 1 year after the initiation of treatment **Adverse events reported:** hyperglycemia, constipation, diarrhea (chronic or transient), acneiform eruption, hyperlipidemia, headache, and increasing fever **Intervals at which outcomes were assessed:** 1, 3, 4, 12 weeks and 1 year
Notes	**Study period:** March 1991 to December 1996 **Funding sources:** not reported **Declarations of interest:** not reported **Reported subgroup analyses:** none reported Information about allocation concealment and outcomes provided by Masato Wakakura

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	“treatment was randomly assigned by the envelope method” – details of envelopes (e.g. sequentially numbered, opaque, sealed, etc.) not reported.
Masking (performance bias and detection bias)	Low risk	"In this study, it was the policy to inform neither the patient nor examiner which treatment was being used, although it was known by the attending physician".
Incomplete outcome data (attrition bias) All outcomes	High risk	“Data for 70 patients were analyzed in the baseline study. Four patients were subsequently eliminated just before the start of treatment (n = 2) or during treatment (n = 2), because they had decided not to give their consent”. “HFA mean deviation could be determined for only 46 cases…Color vision could be examined in 52 eyes in the first 12 weeks of the study…Contrast sensitivity data were obtained for 37 eyes. CFF was measured for 51 eyes” . "No patient was required to drop out of the study".
Selective reporting (reporting bias)	Low risk	Outcomes reported as described in the methods section, though we did not have access to the original trial protocol.
Other bias	Low risk	In both groups, intravenous administrations (systemic) of the drugs were given to the participants, though some data were presented using "eye" as the unit in the analysis.

ONTT 1992-2006

Study characteristics

Methods	**Study design:** parallel group randomized controlled trial

ONTT 1992-2006 *(Continued)*

	Number randomized: 457 total participants: 151 in intravenous methylprednisolone group, 156 in oral prednisone group, and 150 in oral placebo group **Exclusions after randomization:** no exclusions, 9 participants ineligible but randomized and followed **Losses to follow up:** 19 at 6 months; 48 at 1 year **Number analyzed (total and per group):** 438 at 6 months: 144 in intravenous methylprednisolone group, 151 in oral prednisone group, and 143 in oral placebo group **Unit of analysis:** participant **How were the missing data handled?:** excluded from the analyses **Power calculation:** none reported
Participants	**Country:** USA **Age:** mean 32 years (range 18 to 46) **Gender:** 105/457 (23%) men and 352/457 (77%) women **Inclusion criteria:** between the ages of 18 to 46 years; history of acute unilateral optic neuritis with visual symptoms lasting 8 days or less; evidence of a relative afferent pupillary defect and a visual-field defect in the affected eye on examination **Exclusion criteria:** previous diagnosis with optic neuritis in the same eye or had clinical evidence of a systemic disease, other than multiple sclerosis, that might cause optic neuritis **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** intravenous methylprednisolone 250 mg every 6 hours for 3 days followed by 1 mg/kg body weight of oral prednisone for 11 days **Intervention 2:** oral prednisone 1mg/kg/day for 14 days, tapered with administration of 20 mg on day 15 and 10 mg on days 16 and 18 **Intervention 3:** oral placebo 1 mg/kg/day for 14 days with similar treatment as oral corticosteroid group on days 15, 16 and 18 **Length of follow-up:** 12 months
Outcomes	**Primary outcomes, as defined:** (1) Visual field (Humphrey Visual Field Analyzer and Goldmann perimeter) at 6 months (2) Contrast sensitivity (Pelli-Robson chart) at 6 months **Secondary outcomes:** (1) Visual acuity (Retro illuminated ETDRS chart) (2) Color vision (Farnsworth-Munsell 100-hue test) (3) Quality of life: (National Eye Institute Visual Function Questionnaire (NEI-VFQ) - administered 5 to 8 years after initial acute optic neuritis, at 10 to 12 years, and at 15 to 18 years after acute optic neuritis **Adverse events reported:** acute transient depression, acute pancreatitis, sleep disturbance, mild mood change, stomach upset, facial flushing, and weight gain **Intervals at which outcomes were assessed:** days 4, 15, 30; 7, 13, 19 weeks; 6, 12 months, then yearly. The data collected at the 6-month visit was used as the major measurements of visual outcome data
Notes	**Study period:** July 1, 1988 to June 30, 1991

ONTT 1992-2006 *(Continued)*

Funding sources: cooperative agreements with the National Eye Institute, U.S. National Institutes of Health

Declarations of interest: not reported

Reported subgroup analyses: none reported

Data provided by the Jaeb Center for Health Research in personal communication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A permuted-blocks design with a separate sequence for each clinical center was used to assign patients randomly in equal numbers to three treatment groups".
Allocation concealment (selection bias)	Low risk	"Each bottle for the prednisone and placebo groups had a numbered envelope type sealed label, within which the actual contents of the bottle was identified for emergency purposes. On dispensing the medication a portion of the label was torn off and placed in the patient's chart."
Masking (performance bias and detection bias)	Unclear risk	"Patients in the oral-prednisone and placebo groups were blinded to their treatment assignment, whereas those in the intravenous-methylprednisolone group were not". "The personnel assessing visual function were always unaware of whether the patient was assigned to the placebo or prednisone group, and as often as possible they were unaware of whether the patient was receiving methylprednisolone". "When examining visual function in the patients in the intravenous-methylprednisolone group, technicians were unaware of the patient's treatment assignment during 86 percent of all follow-up visits overall and 94 percent of the six-month visits". "Upon completion of treatment, the portion of the label that had been removed was returned to the DCC, which verified that the correct bottle had been dispensed to the patient and that masking had not been compromised (i.e., label intact)".
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The overall rate of visits missed among the seven scheduled follow-up visits in the first six months was 3.4 percent." The reasons for missed follow-up visits not reported.
Selective reporting (reporting bias)	Low risk	"Visual field and contrast sensitivity were the primary measures of outcome; visual acuity and color vision were secondary measures". Outcomes reported as described in the methods section, though we did not have access to the original trial protocol.
Other bias	Unclear risk	Study medication provided by industry.

Sellebjerg 1999

Study characteristics

Methods	**Study design:** parallel group randomized controlled trial

Sellebjerg 1999 *(Continued)*

	Number randomized: 60 total participants: 30 in steroid group and 30 in placebo group **Exclusions after randomization:** none **Losses to follow up:** 0 at 8 weeks; 1 from 8 weeks to 1 year**:** 1 in methylprednisolone group; 8 after 1 year: 4 in methylprednisolone group, 4 in placebo group **Number analyzed (total and per group):** 60 at 8 weeks: 30 in steroid group and 30 in placebo group **Unit of analysis:** participant **Power calculation:** "A formal power calculation was not performed, but based on the results obtained in a previous study, the 60 patients included in the trial were estimated to be sufficient to disclose a clinically relevant treatment effect because we assessed as efficacy measures changes from baseline rather than absolute values."
Participants	**Country:** Denmark **Age:** 27 to 41 **Gender:** 23/60 (38.3%) men and 37/60 (61.7%) women **Inclusion criteria:** participants with optic neuritis; age 18 to 55 years; visual acuity of 0.7 or less (Snellen decimal fraction); duration of no more than 4 weeks **Exclusion criteria:** glucocorticoid treatment within 1 month of trial start; treatment with disease-modifying drugs (e.g., interferons or cytotoxic drugs) within 6 months; pregnancy, lactation, other diseases precluding glucocorticoid treatment; any degree of subjective or objective remission **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** methylprednisolone tablets 500 mg once daily for 5 days, tapering to 400, 300, 200, 100, 64, 48, 32, 16, 8 and 8 mg on each of the 10 following days **Intervention 2:** identical looking tablets for 15 days **Length of follow-up:** 12 months
Outcomes	**Primary outcomes, as defined:** (1) Spatial vision at 1, 3 weeks (2) VAS at 1, 3 weeks (3) The changes in spatial vision at 8 weeks (2) The changes in VAS scores at 8 weeks **Secondary outcomes:** (1) The changes in spatial vision, color vision and VAS scores (2) Normalization of the visual acuity, color vision and contrast sensitivity scores at the individual visits (3) An increase of 1 point in the visual functional system of Kurtzke's Expanded Disability Status Scale based on clinical measurements **Adverse events reported:** gastrointestinal symptoms, insomnia, palpitations, dysphoria or euphoria, hot flashes, edema, musculoskeletal pain, acne, headache, unpleasant or metallic taste, weight gain **Intervals at which outcome were assessed:** 1, 3, 8 weeks and 12 months

Sellebjerg 1999 *(Continued)*

Notes	**Study period:** August 1993 to January 1997 **Funding sources:** grants from the Danish Multiple Sclerosis Society, the Johnsen Memorial Foundation, and Pharmacia & Upjohn **Declarations of interest:** not reported **Reported subgroup analyses:** yes, "… post hoc subgroup analyses suggested that patients with a more severe baseline visual deficit had a somewhat more pronounced response to high-dose methylprednisolone treatment"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Individual randomization in blocks of 10 was performed by the producer using a random numbers table. Consecutive patients were allocated to consecutive randomization numbers in each stratum”.
Allocation concealment (selection bias)	Low risk	“The treatment assignment of each patient was concealed in a numbered, sealed envelope at the department of neurology and was not opened by the investigators before all patients had completed the trial”
Masking (performance bias and detection bias)	Unclear risk	"The treatment assignment of each patient was concealed in a numbered, sealed envelope at the department of neurology and was not opened by the investigators before all patients had completed the trial." “Visual function was tested by a technician unaware of the clinical status of the patient”.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Five patients in the methylprednisolone group and four placebo-treated patients did not participate in the 1-year follow-up study. Follow-up data on one patient from each treatment arm was censored because interferon treatment was initiated within 1 year", but the percentage is higher than 10%. "One patient in the methylprednisolone group discontinued treatment after 4 days due to nausea, migraine, and diarrhea. Another methylprednisolone-treated patient discontinued treatment after 10 days due to heartburn, abdominal discomfort, palpitations, dysphoria, and insomnia. One patient in the placebo group discontinued treatment after 2 days due to vertigo, vomiting, and headache, presumably caused by a demyelinating lesion in the brainstem". Trial reported intention-to-treat analysis in the methods but performed available cases analyses.
Selective reporting (reporting bias)	Low risk	"The four primary efficacy measures were the spatial vision and VAS scores at the 1-week and 3-week visits". "Secondary outcome measures were changes in spatial vision, color vision, and VAS scores; normalization of the visual acuity, color vision, and contrast sensitivity scores at the individual visits; and an increase of one point in the visual functional system of Kurtzke’s Expanded Disability Status Scale (EDSS)". "The primary efficacy measures were chosen before unblinding. In patients with bilateral symptoms only, the results obtained in the eye with the worse baseline visual acuity were analyzed".
Other bias	Unclear risk	"Supported by grants from the Danish Multiple Sclerosis Society, the Johnsen Memorial Foundation, and Pharmacia & Upjohn."

Tübingen Study 1993

Study characteristics	
Methods	**Study design:** parallel group RCT (44 participants) and non-RCT (12 participants who selected treatment group) **Number randomized:** 44 total participants; 17 in prednisolone group and 27 in vitamin B1 group **Exclusions after randomization:** 6 due to poor adherence: 3 in prednisolone group and 3 in vitamin B1 group **Losses to follow up:** 3 at 6 months: 1 in prednisolone group and 2 in vitamin B1 group; 6 at 12 months: 3 in prednisolone group and 3 in vitamin B1 group **Number analyzed:** 35 RCT participants at 6 months (13 in prednisolone group and 22 in vitamin B1 group) plus 12 non-RCT participants at 6 months (2 in prednisolone group and 10 in vitamin B1 group) **Unit of analysis:** participant **How were missing data handled?:** excluded from the analyses **Power calculation:** none reported
Participants	**Country:** Germany **Age:** 30 years **Gender:** 14/50 (28%) men and 36/50 (72%) women **Inclusion criteria:** acute unilateral optic neuritis of presumed demyelinative origin; maximal disease duration of 3 weeks; without any improvement since onset; first attack in the involved eye/no previous history of ON; no previous treatment with corticosteroids; no acute symptoms of multiple sclerosis present **Exclusion criteria:** not reported **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** oral methylprednisolone 100, 80, 60, 40, 30, 20, 10, 5 mg for 3 days each **Intervention 2:** oral vitamin B1 **Length of follow-up:** follow up at 1, 2, 3, 4, 6, 8 weeks and 3, 4, 5, 6, 9, 12 months
Outcomes	**Primary and secondary outcomes were not differentiated** **Outcomes as reported:** (1) Profile perimetry: a nearly normal level was reached when the light difference sensitivity was reduced by 2 to 3 decibel (2) Kinetic perimetry: was defined as normal when the isopter for 0.63 candela/m^2 was situated at 1 to 2 degree, the isopter for 1 candela/m^2 at 5 degree (3) Visual acuity: complete normalization was reached in 1.0 to 1.25 (20/20 to 20/16), nearly normal level was defined when it reached 0.8 (20/25) (4) Aulhorn flicker test: the flicker test result was categorized as nearly normal when the two criteria were no longer fulfilled

Tübingen Study 1993 *(Continued)*

	Adverse events reported: acne **Intervals at which outcomes were assessed:** all participants were monitored for 1, 2, 3, 4, 6, 8 weeks and 3, 4, 5, 6, 9, 12 months for follow up; neurological examination was performed in the first week and after 3 months
Notes	**Study period:** between 1980 and 1986 **Funding sources:** Hoechst and Goedecke/Parke-Davis Pharma Industries and by H. and L. Schilling Foundation, TS 013/54/87 **Declarations of interest:** not reported **Reported subgroup analyses:** not performed; "A detailed analysis of these questions is not possible in this study, because when our group is divided into subgroups, the samples' size becomes too small for statistical evaluation. The limitation by sample size is mainly due to the strict criteria for patient selection (see Methods) and to the fact that fewer patients are available in one single centre"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"In addition, 12 ON patients who refused to participate under double-blind conditions, were treated in an unmasked manner, two with methylprednisolone and 10 with vitamin B1 according to their own choice."
Allocation concealment (selection bias)	High risk	"In addition, 12 ON patients who refused to participate under double-blind conditions, were treated in an unmasked manner, two with methylprednisolone and 10 with vitamin B1 according to their own choice."
Masking (performance bias and detection bias)	High risk	"In addition, 12 ON patients who refused to participate under double-blind conditions, were treated in an unmasked manner, two with methylprednisolone and 10 with vitamin B1 according to their own choice." "In all patients their treatment assignment was not known during data evaluation."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Exclusion of 6 participants after randomization due to poor treatment compliance; 3 in corticosteroid arm (3/17) and 3 in placebo arm (3/27).
Selective reporting (reporting bias)	Low risk	Outcomes reported as described in the methods section, though we did not have access to the original trial protocol.
Other bias	High risk	Funded by pharmaceutical industry. There was a deviation from randomization: 12 participants chose the assignment according to their decision (2 in methylprednisolone group and 10 in vitamin B1 group).

IV: intravenous
IVMP: intravenous methylprednisolone
RCT: randomized controlled trial
MRI: magnetic resonance imaging
VEP: visual evoked potential
ETDRS: Early Treatment Diabetic Retinopathy Study
HFA: Humphrey Field Analyzer
VAS: visual analog scale

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

Study	Reason for exclusion
Al-Eajailat 2014	This article is a report of a trial with no clear information for randomization. Could not reach the author for further information
Alejandro 1994	This article was translated and reviewed. It describes a study that examined two routes of administration of corticosteroids and hence is outside the scope of this review
Beran 1973	This article is a retrospective comparison of those treated by glucocorticosteroids and foreign protein therapy
Bhatti 2005	This article is a review with no additional trials
Bird 1976	This article is a review and describes studies that were already reviewed by the authors of this study
Bowden 1974	Evaluated adrenocorticotropic hormone, a precursor of corticosteroids
Brusa 1999	This article examines a convenience sample from an RCT and hence does not satisfy the inclusion criteria for this review
Brusaferri 2000	This article is a meta-analysis of RCT on steroid treatment for optic neuritis. The articles included in this paper have already been reviewed by the authors of this review and determined not to contain additional data
Chuman 2004	This article reports a discussion of one of the included trials
Gould 1977	This trial originally was selected for inclusion in the review, but after further assessment we excluded it because of inadequate randomization method. This trial compared a single injection of triamcinolone into the orbit versus no injection
Hallermann 1983	This study is not an RCT and hence does not satisfy the inclusion criteria for this review
Hickman 2002	Trial was not initiated as per personal communication with Dr. Hickman
Kommerell 1994	Summary and discussion of ONTT 1992-2006
Kott 1997	The intervention 'copaxone' is an amino acid polymer, not a corticosteroid and hence outside the scope of this review
Midgard 2005	This article was translated and was determined not to be an RCT (retracted literature review)
Park 2013	This is a randomized controlled trial with 30 included patients, but the study compared retrobulbar triamcinolone injection versus treatment from conventional ONTT protocol, which is outside the scope of this review
Pirko 2004	This is not an RCT; discusses natural history of optic neuritis
Rawson (1966-69)	Evaluated adrenocorticotropic hormone, a precursor of corticosteroids
Roed 2005	Compares interventions not eligible for inclusion in this review
Soderstrom 1995	This article was translated; not an RCT
Toczolowski 1995	This article was translated; not an RCT

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

NCT01524250

Study name	Optic Neuritis Recovery After Oral or IV Corticosteroids
Methods	**Study design:** RCT (parallel assignment) **Estimated enrollment:** 46 participants **Study centers:** London Health Sciences Center and St. Joseph's Health Care Center in London, Ontario, Canada **Length of follow-up:** 6 months
Participants	**Inclusion criteria:** age 18 to 65 years; unilateral acute demyelinating optic neuritis; within 14 days of symptom onset; visual acuity in study eye of 20/40 or better **Exclusion criteria:** received corticosteroids within 30 days; change in dose of any medication taken for comorbid conditions; any medical condition affecting visual acuity; history of optic neuritis in study eye
Interventions	**Intervention 1:** 1250 mg oral prednisone daily for 3 days **Intervention 2:** 1000 mg IV methylprednisolone daily for 3 days
Outcomes	**Primary outcome, as defined:** P100 latency of the Visual Evoked Potential in the study eye at 6 months **Secondary outcomes, as defined:** high contrast visual acuity at one and six months; contrast sensitivity at one and six months; P100 latency of the Visual Evoked Potential in the study eye at one month **Intervals at which outcomes to be assessed:** one and six months post-corticosteroid treatment
Starting date	March 2012 (estimated completion September 2016)
Contact information	Sarah A Morrow, MD, FRCPC, MSc; London Health Sciences Center
Notes	**Funding source:** London Health Sciences Centre and The Physicians' Services Incorporated Foundation

NCT01838174

Study name	A Phase IV Trial of Neuroprotection With ACTH in Acute Optic Neuritis (ACTHAR)
Methods	**Study design:** RCT (parallel assignment) **Estimated enrollment:** 60 participants **Study centers:** University of Texas Southwestern Medical Center; University of Colorado Denver **Length of follow-up:** six months
Participants	**Inclusion criteria:** age 18 to 55 years; diagnosed with clinically unilateral acute demyelinating optic neuritis; within 14 days of symptom onset prior to intended randomization; the qualifying episode of optic neuritis must be the first clinical episode of optic neuritis in the affected eye; ability to undergo treatment with intravenous methylprednisolone or Acthar gel

NCT01838174 *(Continued)*	
	Exclusion criteria: functionally or clinically relevant comorbidity of the affected eye; bilateral optic neuritis; concurrent functionally or clinically relevant disturbances of the eye not affected by acute demyelinating optic neuritis (ADON); high clinical likelihood of a form of optic neuritis other than ADON; non-assessable ocular coherence tomography (OCT) at screening; refractive error greater than ±5 diopters or pre-surgical value to be used for patients having undergone refractive surgery; an immune system disorder other than Multiple Sclerosis (MS) or ADON or with a known immunodeficiency syndrome; prior treatment with IV methylprednisolone (IVMP) or Acthar gel within the past 30 days; treatment with rituximab, mitoxantrone, cyclophosphamide, mycophenolate, azathioprine, alemtuzumab, ocrelizumab, or other non-approved agents for the treatment of relapsing forms of MS; concurrent use of 4-aminopyridine
Interventions	**Intervention 1:** Acthar Gel (ACTH) 15 days of daily injections **Intervention 2:** IV steroids with oral taper (3 days of intravenous methylprednisolone followed by 11 days of oral taper, details for oral taper not provided)
Outcomes	**Primary outcome, as defined:** retinal nerve fiber layer (RNFL) thickness at 6 months **Secondary outcomes, as defined:** the frequency of optic nerves with RNFL swelling between the IV methylprednisolone-treated and Acthar-treated groups at 1 and 3 months **Intervals at which outcomes to be assessed:** at months 1, 3, and 6
Starting date	May 2013 (estimated completion April 2015)
Contact information	Gina Remington, RN, BSN (214-645-0560; gina.remington@utsouthwestern.edu)
Notes	No funding source given

IV: intravenous
RCT: randomized controlled trial

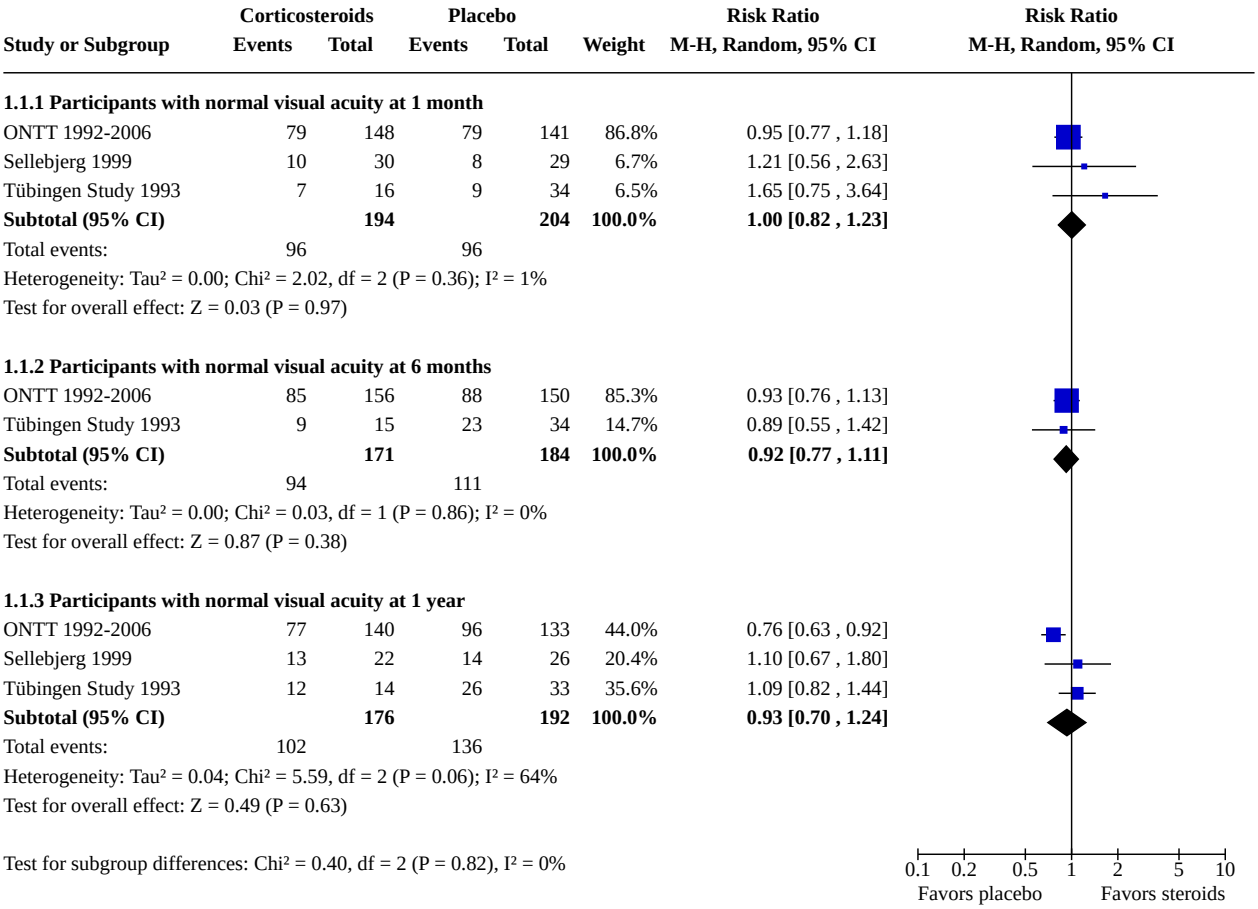
DATA AND ANALYSES

Comparison 1. Oral corticosteroids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Participants with normal visual acuity	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1.1 Participants with normal visual acuity at 1 month	3	398	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.82, 1.23]
1.1.2 Participants with normal visual acuity at 6 months	2	355	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.11]
1.1.3 Participants with normal visual acuity at 1 year	3	368	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.70, 1.24]
1.2 Participants with contrast sensitivity in the normal range	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2.1 Participants with contrast sensitivity in the normal range at 1 month	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

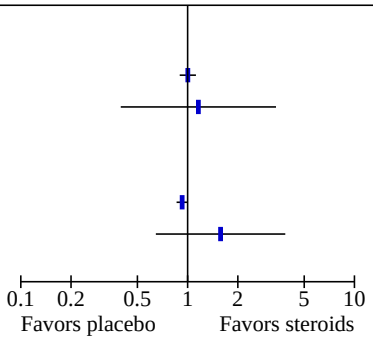
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.2 Participants with contrast sensitivity in the normal range at 1 year	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.3 Participants with normal visual field	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.3.1 Participants with normal visual field at 1 month	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.3.2 Participants with normal visual field at 6 months	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.3.3 Participants with normal visual field at 1 year	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Oral corticosteroids versus placebo, Outcome 1: Participants with normal visual acuity



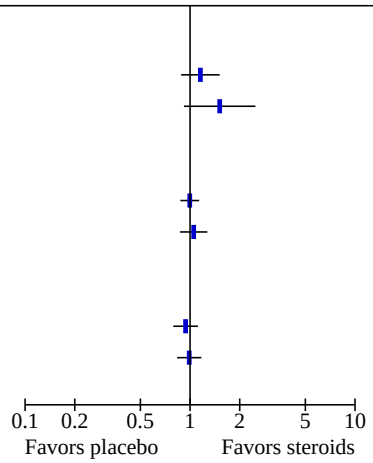
Analysis 1.2. Comparison 1: Oral corticosteroids versus placebo, Outcome 2: Participants with contrast sensitivity in the normal range

Study or Subgroup	Corticosteroids Events	Corticosteroids Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
1.2.1 Participants with contrast sensitivity in the normal range at 1 month					
ONTT 1992-2006	120	148	114	141	1.00 [0.90 , 1.12]
Sellebjerg 1999	6	30	5	29	1.16 [0.40 , 3.39]
1.2.2 Participants with contrast sensitivity in the normal range at 1 year					
ONTT 1992-2006	122	140	125	133	0.93 [0.86 , 1.00]
Sellebjerg 1999	8	22	6	26	1.58 [0.64 , 3.85]



Analysis 1.3. Comparison 1: Oral corticosteroids versus placebo, Outcome 3: Participants with normal visual field

Study or Subgroup	Corticosteroids Events	Corticosteroids Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
1.3.1 Participants with normal visual field at 1 month					
ONTT 1992-2006	67	146	56	141	1.16 [0.88 , 1.51]
Tübingen Study 1993	11	16	15	33	1.51 [0.92 , 2.49]
1.3.2 Participants with normal visual field at 6 months					
ONTT 1992-2006	116	156	112	150	1.00 [0.87 , 1.14]
Tübingen Study 1993	13	14	30	34	1.05 [0.87 , 1.27]
1.3.3 Participants with normal visual field at 1 year					
ONTT 1992-2006	89	140	90	133	0.94 [0.79 , 1.12]
Tübingen Study 1993	13	14	31	33	0.99 [0.83 , 1.17]



Comparison 2. Total intravenous corticosteroid dose more than or equal to 3000 mg versus placebo

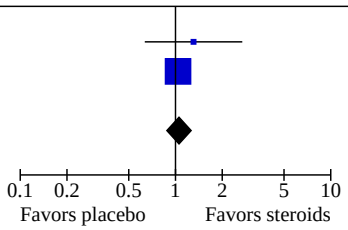
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Participants with normal visual acuity at 6 months	2	346	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.88, 1.26]
2.2 Participants with contrast sensitivity in the normal range sensitivity at 1 month	2	322	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.74, 2.16]
2.3 Participants with contrast sensitivity in the normal range at 6 months	2	346	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.92, 1.33]
2.4 Participants with contrast sensitivity in the normal range at 1 year	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 Participants with normal visual field at 1 month	2	330	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.88, 2.76]
2.6 Participants with normal visual field at 6 months	2	346	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.96, 1.21]
2.7 Participants with normal visual field at 1 year	2	316	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.86, 1.19]

Analysis 2.1. Comparison 2: Total intravenous corticosteroid dose more than or equal to 3000 mg versus placebo, Outcome 1: Participants with normal visual acuity at 6 months

	Corticosteroids		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Kapoor 1998	10	22	8	23	6.2%	1.31 [0.63 , 2.69]	
ONTT 1992-2006	92	151	88	150	93.8%	1.04 [0.86 , 1.25]	
Total (95% CI)		**173**		**173**	**100.0%**	**1.05 [0.88 , 1.26]**	
Total events:	102		96				

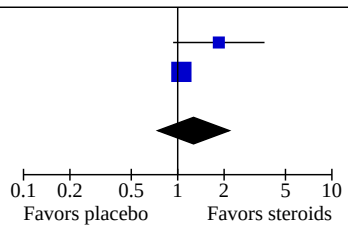
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Total intravenous corticosteroid dose more than or equal to 3000 mg versus placebo, Outcome 2: Participants with contrast sensitivity in the normal range sensitivity at 1 month

	Favours placebo		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
ONMRG 1999	9	14	8	23	32.5%	1.85 [0.93 , 3.66]	
ONTT 1992-2006	123	144	114	141	67.5%	1.06 [0.95 , 1.17]	
Total (95% CI)		**158**		**164**	**100.0%**	**1.27 [0.74 , 2.16]**	
Total events:	132		122				

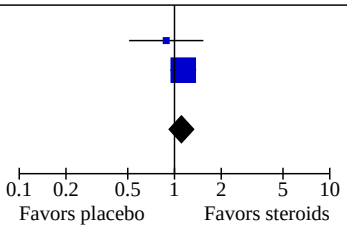
Heterogeneity: Tau² = 0.11; Chi² = 2.72, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Total intravenous corticosteroid dose more than or equal to 3000 mg versus placebo, Outcome 3: Participants with contrast sensitivity in the normal range at 6 months

Study or Subgroup	Corticosteroids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kapoor 1998	11	22	13	23	10.8%	0.88 [0.51 , 1.53]
ONTT 1992-2006	94	151	82	150	89.2%	1.14 [0.94 , 1.38]
Total (95% CI)		**173**		**173**	**100.0%**	**1.11 [0.92 , 1.33]**
Total events:	105		95			

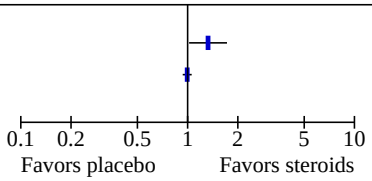
Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Total intravenous corticosteroid dose more than or equal to 3000 mg versus placebo, Outcome 4: Participants with contrast sensitivity in the normal range at 1 year

Study or Subgroup	Corticosteroids Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
ONMRG 1999	14	14	17	23	1.33 [1.02 , 1.72]
ONTT 1992-2006	128	137	125	133	0.99 [0.93 , 1.06]

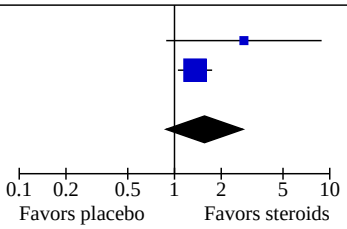
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Total intravenous corticosteroid dose more than or equal to 3000 mg versus placebo, Outcome 5: Participants with normal visual field at 1 month

Study or Subgroup	Corticosteroids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ONMRG 1999	10	25	3	21	19.4%	2.80 [0.88 , 8.86]
ONTT 1992-2006	77	143	56	141	80.6%	1.36 [1.05 , 1.75]
Total (95% CI)		**168**		**162**	**100.0%**	**1.56 [0.88 , 2.76]**
Total events:	87		59			

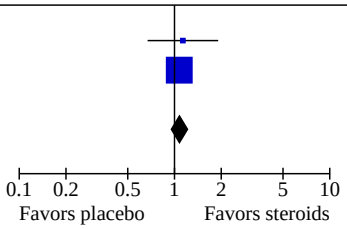
Heterogeneity: Tau² = 0.09; Chi² = 1.48, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 1.53 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Total intravenous corticosteroid dose more than or equal to 3000 mg versus placebo, Outcome 6: Participants with normal visual field at 6 months

Study or Subgroup	Corticosteroids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kapoor 1998	13	22	12	23	5.2%	1.13 [0.67 , 1.91]
ONTT 1992-2006	121	151	112	150	94.8%	1.07 [0.95 , 1.21]
Total (95% CI)		**173**		**173**	**100.0%**	**1.08 [0.96 , 1.21]**
Total events:	134		124			

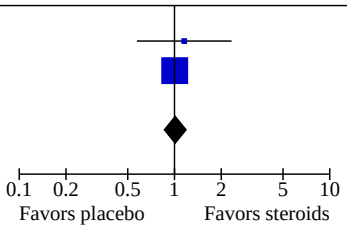
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Total intravenous corticosteroid dose more than or equal to 3000 mg versus placebo, Outcome 7: Participants with normal visual field at 1 year

Study or Subgroup	Corticosteroids Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ONMRG 1999	11	25	8	21	5.2%	1.16 [0.57 , 2.33]
ONTT 1992-2006	93	137	90	133	94.8%	1.00 [0.85 , 1.18]
Total (95% CI)		**162**		**154**	**100.0%**	**1.01 [0.86 , 1.19]**
Total events:	104		98			

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Optic Neuritis
#2 (optic* or retrobul*) near/2 (neuritis)
#3 (#1 OR #2)
#4 MeSH descriptor Adrenal Cortex Hormones
#5 MeSH descriptor Glucocorticoids
#6 glucocorticoid*
#7 MeSH descriptor Pregnadienediols
#8 prednisone*
#9 prednisolone*
#10 methylprednisolone*
#11 triamcinolone*
#12 dexamethasone*
#13 anecortave*
#14 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 (#3 AND #14)

Appendix 2. MEDLINE (OvidSP) search strategy

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.

6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp optic neuritis/
13. ((optic* or retrobul*) adj2 neuritis).tw.
14. or/12-13
15. exp adrenal cortex hormones/
16. exp glucocorticoids/
17. glucocorticoid*.tw.
18. exp pregnadienediols/
19. prednisone*.tw.
20. prednisolone*.tw.
21. methylprednisolone*.tw.
22. triamcinolone*.tw.
23. dexamethasone*.tw.
24. anecortave*.tw.
25. or/15-24
26. 14 and 25
27. 11 and 26

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al (Glanville 2006).

Appendix 3. EMBASE.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'optic neuritis'/exp
#34 ((optic* OR retrobul*) NEAR/2 neuritis):ab,ti
#35 #33 OR #34

#36 'corticosteroid'/exp
#37 'glucocorticoid'/exp
#38 glucocorticoid*:ab,ti
#39 prednisone*:ab,ti
#40 prednisolone*:ab,ti
#41 methylprednisolone*:ab,ti
#42 triamcinolone*:ab,ti
#43 dexamethasone*:ab,ti
#44 'pregnane derivative'/exp
#45 'anecortave'/exp
#46 anecortave*:ab,ti
#47 #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46
#48 #35 AND #47
#49 #32 AND #48

Appendix 4. LILACS search strategy

MH:C10.292.700.550$ or MH:C11.640.576$ or "Neuritis Óptica" or "Neurite Óptica" or "Retrobulbar Neuritis" or ((optic or retrobul$) and neuritis)

Appendix 5. PubMed search strategy

#1 ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
#2 ((optic*[tw] OR retrobul*[tw]) AND (neuritis[tw])) NOT Medline[sb]
#3 glucocorticoid*[tw] NOT Medline[sb]
#4 prednisone*[tw] NOT Medline[sb]
#5 prednisolone*[tw] NOT Medline[sb]
#6 methylprednisolone*[tw] NOT Medline[sb]
#7 triamcinolone*[tw] NOT Medline[sb]
#8 dexamethasone*[tw] NOT Medline[sb]
#9 anecortave*[tw] NOT Medline[sb]
#10 (#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 (#2 AND #10)
#12 (#1 AND #11)

Appendix 6. *meta*Register of Controlled Trials search strategy

Optic Neuritis AND (Corticosteroids OR Adrenal Cortex Hormones OR Glucocorticoids OR Pregnadienediols OR Prednisone OR Prednisolone OR Methylprednisolone OR Triamcinolone OR Dexamethasone OR Anecortave)

Appendix 7. ClinicalTrials.gov search strategy

Optic Neuritis AND (Corticosteroids OR Adrenal Cortex Hormones OR Glucocorticoids OR Pregnadienediols OR Prednisone OR Prednisolone OR Methylprednisolone OR Triamcinolone OR Dexamethasone OR Anecortave)

Appendix 8. ICTRP search strategy

Optic Neuritis AND Corticosteroids OR Optic Neuritis AND Adrenal Cortex Hormones OR Optic Neuritis AND Glucocorticoids OR Optic Neuritis AND Pregnadienediols OR Optic Neuritis AND Prednisone OR Optic Neuritis AND Prednisolone OR Optic Neuritis AND Methylprednisolone OR Optic Neuritis AND Triamcinolone OR Optic Neuritis AND Dexamethasone OR Optic Neuritis AND Anecortave

WHAT'S NEW

Date	Event	Description
11 November 2021	Amended	Editorial note added. See Published notes for further information.

HISTORY

Protocol first published: Issue 1, 1999
Review first published: Issue 1, 2007

Date	Event	Description
29 July 2015	New citation required but conclusions have not changed	Issue 8, 2015: No new trials found for inclusion; one additional ongoing study identified
9 April 2015	New search has been performed	Issue 8, 2015: Electronic searches were updated.
27 February 2012	New citation required but conclusions have not changed	Issue 4, 2012: Some of the text of the review has been modified to reflect the methodological changes made by The Cochrane Collaboration.
27 February 2012	New search has been performed	Issue 4, 2012: Updated searches yielded one new trial for inclusion.
27 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

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Coordinating the review: SBF, SSV
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- Designing search strategies: RG, SBF, Karen Blackhall, Iris Gordon, Lori Rosman
- Undertaking searches: Karen Blackhall, Iris Gordon, Lori Rosman
- Screening search results: SBF, RG
- Organizing retrieval of papers: SBF, RG
- Screening retrieved papers against inclusion criteria: SBF, RG
- Appraising quality of papers: SBF, RG, SSV
- Extracting data from papers: SBF, RG
- Writing to authors of papers for additional information: SBF, SSV
- Providing additional data about papers: SBF, SSV
- Obtaining and screening data on unpublished studies: RG, SBF

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- Providing a clinical perspective: RB
- Providing a policy perspective: RB
- Providing a consumer perspective: SBF, RG, SSV, RB

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Guarantor for review: RG

Updating the review: RG, SSV, Cochrane Eyes and Vision Group US Project

DECLARATIONS OF INTEREST

Roy Beck is the primary investigator for the Optic Neuritis Treatment Trial.

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- Johns Hopkins University, USA

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  The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Cochrane methodology regarding assessments of the risk of bias in included studies have been modified and the review authors updated the 'Assessment of risk of bias in included studies' section of the methods to reflect updated methodological considerations.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Anti-Inflammatory Agents [administration & dosage] [*therapeutic use]; Contrast Sensitivity [drug effects]; Dexamethasone [administration & dosage] [therapeutic use]; Glucocorticoids [administration & dosage] [*therapeutic use]; Injections, Intravenous; Methylprednisolone [administration & dosage] [therapeutic use]; Optic Neuritis [*drug therapy]; Prednisone [administration & dosage] [therapeutic use]; Randomized Controlled Trials as Topic; Visual Acuity [drug effects]

MeSH check words

Female; Humans; Male