Antiviral treatment for Bell's palsy (idiopathic facial paralysis)

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[Intervention Review]

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ABSTRACT

Background

Antiviral agents against herpes simplex virus are widely used in the treatment of idiopathic facial paralysis (Bell's palsy), but their effectiveness is uncertain. Significant morbidity can be associated with severe cases.

Objectives

This review addresses the effect of antiviral therapy on Bell's palsy.

Search methods

We updated the search of the Cochrane Neuromuscular Disease Group Trials Register (December 2008), MEDLINE (from January 1966 to December 8 2008), EMBASE (from January 1980 to December 8 2008) and LILACS (from January 1982 to December 2008).

Selection criteria

Randomized trials of antivirals with and without corticosteroids versus control therapies for the treatment of Bell's palsy.

Data collection and analysis

Twenty-three papers were selected for consideration.

Main results

Seven trials including 1987 participants met the inclusion criteria, adding five studies to the two in the previous review.

Incomplete recovery at one year. There was no significant benefit in the rate of incomplete recovery from antivirals compared with placebo (n = 1886, RR 0.88, 95% CI 0.65 to 1.18). In meta-analyses with some unexplained heterogeneity, the outcome with antivirals was significantly worse than with corticosteroids (n = 768, RR 2.82, 95% CI 1.09 to 7.32) and the outcome with antivirals plus corticosteroids was significantly better than with placebo (n = 658, RR 0.56, 95% CI 0.41 to 0.76).

Motor synkinesis or crocodile tears at one year. In single trials, there was no significant difference in long term sequelae comparing antivirals and corticosteroids with corticosteroids alone (n = 99, RR 0.39, 95% CI 0.14 to 1.07) or antivirals with corticosteroids (n = 101, RR 1.03, 95% CI 0.51 to 2.07).

Adverse events. There was no significant difference in rates of adverse events between antivirals and placebo (n = 1544, RR 1.06, 95% CI 0.81 to 1.38), between antivirals and corticosteroids (n = 667, RR 0.96, 95% CI 0.65 to 1.41) or between the antiviral-corticosteroid combination and placebo (n = 658, RR 1.15, 95% CI 0.79 to 1.66).

Authors' conclusions

High quality evidence showed no significant benefit from anti-herpes simplex antivirals compared with placebo in producing complete recovery from Bell's palsy. Moderate quality evidence showed that antivirals were significantly less likely than corticosteroids to produce complete recovery.

PLAIN LANGUAGE SUMMARY

Antiviral treatment for Bell's palsy

Bell's palsy is a disease of the facial nerve which causes one side of the face to be paralysed. Some studies have suggested that it is caused by infection with the cold sore (herpes simplex) virus. If this is correct, antiviral drugs against herpes simplex would be likely to help recovery. It has also been suggested that corticosteroids may help. The paralysis is usually temporary even when untreated, although without treatment about one person in five is left with permanent facial disfigurement or pain.

This updated review provided high quality evidence that antivirals are no more effective than placebo (dummy) treatment in producing complete recovery. On the other hand moderate quality evidence showed that antivirals were less effective than corticosteroids and that combined antiviral-corticosteroid treatment were more effective than placebo. Taken together, these results suggest that corticosteroids might be effective but this requires confirmation from the Cochrane review of corticosteroids which is being updated. There was no evidence that antivirals produced significantly more or significantly fewer adverse events than dummy treatment.

As this analysis shows that antivirals against the cold sore virus are not significantly effective, other causes for Bell's palsy than infection by the cold sore virus now need to be considered.

BACKGROUND

Bell's palsy is an acute unilateral paralysis of the facial nerve first described by the Scottish surgeon Sir Charles Bell (1774 to 1842) (Petruzelli 1991). It affects 11 to 40 people per 100,000 in the population per annum, most commonly in the age group 30 to 45 (Bateman 1992; Brandenberg 1993; Katusic 1986; Pietersen 1982; Pietersen 2002; Yanagihara 1988). The condition presents disproportionately amongst pregnant women and people who have diabetes, influenza, a cold, or some other upper respiratory ailment. On average, every year a British general practitioner will see one or two people who have developed the condition. A UK study using the general practice research database (GPRD) showed that 36% of people were treated with oral corticosteroids and 19% were referred to hospital (Rowlands 2002). Although most recover well, 30% of people with Bell's palsy have a poor recovery with continuing facial disfigurement, psychological difficulties and sometimes facial pain (though the presence and course of pain is unclear from current knowledge) (Morgenlander 1990). The aetiology has yet be established but genetic, vascular, infectious and immunological causes have all been postulated (Adour 1996). Animal studies have suggested the possibility that reactivation of herpes viruses may be responsible for demyelination (Morgan 1995; Sugita 1995). Herpes simplex virus, has been implicated as a cause in several studies (McCormick 1972; Murakami 1996; Stjernquist-Desatnik 2006; Takasu 1992; Theil 2001). Infection with this virus is thought to cause inflammation of the facial nerve. Treatment has commonly been based on this hypothesis. Antiviral medication is supposed to eradicate the infectious agent and corticosteroids to reduce the swelling of the facial nerve.

The previous versions of the Cochrane reviews concerning the treatment of Bell's palsy examined the effectiveness of oral prednisolone and aciclovir (Allen 2007; Salinas 2002). These found that insufficient data exist to conclude that either or both therapies are effective. Many of the studies mentioned in these reviews but excluded from the analysis either failed to randomize participants or, when correctly randomized, were erroneously interpreted in a favourable light (May 1976; Wolf 1978). In addition, high dose corticosteroid therapy has numerous potential side effects including peptic ulceration hypertension and confusional states. Antivi-

ral therapy is expensive and should be reserved for circumstances where definite benefits are likely to be obtained. Previous recommendations suggested that aciclovir needs to be started within 48 hours, although a study of viral replication in participants with Bell's palsy suggested that the window might be extended (Abiko 2002).

Since publication of the previous versions of the Cochrane reviews, large scale, randomized controlled trials of antivirals and corticosteroids have been published necessitating substantive updates of the reviews.

OBJECTIVES

The objective of the review was to determine the effectiveness of anti-herpes simplex antiviral treatments for Bell's palsy. We selected as outcome variables (i) recovery status measured by conventional validated instruments and (ii) presence of motor synkinesis or crocodile tears. A third outcome variable, adverse effects of treatment, was also collected. Other symptoms (pain, discomfort and embarrassment) have been reported as outcomes in some trials but were not considered in this review.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for all randomized or quasi-randomized (alternate or other systematic allocation) controlled trials involving aciclovir, valaciclovir or famciclovir alone or in combination with any other therapy in the treatment of Bell's palsy.

Types of participants

We considered all trials where participants were diagnosed with unilateral facial paralysis of unknown cause, and who satisfied the authors' requirements for eligibility and inclusion.

Types of interventions

We considered all trials where treatment was undertaken with any oral antiviral licensed for the treatment of herpes simplex infections in immunocompetent participants. The list comprised aciclovir, valaciclovir, a pro-drug of aciclovir and famciclovir, a prodrug of penciclovir. We considered trials where participants received antiviral therapy versus placebo or any other treatment.

Types of outcome measures

The outcome measures have been modified since the previous review to take into account the heterogeneity of this group of studies.

Where outcome measures were measured 'at six months', this has been replaced by 'at the end of the study'. Duration of studies included in this review ranges from three months to 12 months: this method allows maximum data inclusion.

Incomplete recovery has been altered to include the range of definitions used by the studies included to allow maximum data capture: as opposed to the previous definition of moderate dysfunction, the term now includes participants with a lack of full function. More participants will be classified as 'incomplete recovery' by this definition.

'Adverse events attributable to antiviral treatment' has been replaced with 'adverse events': in studies where both agents are administered it is difficult to assess which agent is causing the adverse event. Similarly, even when only an antiviral is being prescribed, it is difficult to know whether a specific event should be attributed to the medication or another intercurrent cause. The level of detailed analysis of adverse events in studies did not permit such a judgement being made.

Primary outcomes

Incomplete recovery of facial function at the end of study measured using a validated rating scale.

Secondary outcomes

1. Motor synkinesis or crocodile tears at the end of the study.
2. Complete facial paralysis at the end of the study.
3. Adverse events.

Search methods for identification of studies

In this updated review, we searched the Cochrane Neuromuscular Disease Group Trials register (December 2008), MEDLINE (January 1966 to December 8 2008), EMBASE (January 1980 to December 8 2008) and LILACS (January 1982 to December 2008). We also reviewed the bibliographies of the identified trials, contacted trial authors and known experts in the field and contacted relevant drug companies to identify additional published or unpublished data. For MEDLINE, EMBASE and LILACS database search strategies please see Appendix 1, Appendix 2 and Appendix 3.

Data collection and analysis

All five authors scrutinised the search databases to determine papers for inclusion. At least two authors independently assessed

each paper for relevance, eligibility and quality. There were no disagreements about inclusion.

In the first version of this review four possible trials were identified but only two qualified for inclusion. The number of references retrieved from each source was not stated. A search at the update in April 2003 generated 49 papers in EMBASE, 22 in MEDLINE and 15 in LILACS but no new trials were identified. Our new search in 2008 identified 68 papers in EMBASE, 26 in MEDLINE and 3 in LILACS. From this search, 23 papers were selected for review of the full text and five trials were subsequently included in addition to those which were included in the previous version of the review.

We considered each trial design and whether it was randomized, method of randomization to treatment, dosage of all treatment comparisons (amount, frequency, duration and route of administration), whether the trial was placebo-controlled, blinded (for treatment administrator, patient and assessment of recovery status) or unstated, and for definition of recovery status. All five authors were given a selection of papers to read, review for quality and extract data from. Each trial was assessed by at least two authors. PL completed the risk of bias table which was individually reviewed by FS and FD. All five authors agreed data extraction. Two authors (PL and FD) agreed input into Review Manager (RevMan, the programme provided by the Cochrane Collaboration).

Three of the trial authors were contacted for additional information and two responded with data. A previous review author was contacted for updated information on other studies and a response was received.

Assessment of bias was conducted by scoring studies using the risk of bias methods described in the 2008 version of the Cochrane Handbook.according to Cochrane methods.

We calculated a weighted treatment effect using the Mantel-Haenszel method (Egger 2007). The random effects model was used where there was marked heterogeneity between studies (Chi^2 test, $P < 0.1$, $I^2 > 50\%$). The fixed-effect model was used where heterogeneity was not detected with standard statistical methods.

When comparing studies which use differing symptom scores to assess outcome, we used the House-Brackman scale when available as this was the most widely used or had comparisons to other scales available.

When assessing adverse events, the number of participants affected, as opposed to the number of events was used to facilitate data comparison.

As in previous editions of this review, the meta-analysis outcomes have been reported for both studies which compare antivirals either with or without corticosteroids to corticosteroids and those studies which compare antivirals only to corticosteroids only. We have conducted three comparisons: antivirals versus placebo (including antivirals plus corticosteroids versus placebo plus corticosteroids and antivirals plus corticosteroids versus no treatment plus corticosteroids), antivirals versus corticosteroids and antivirals plus corticosteroids versus placebo.

Sensitivity analysis has been used to assess the effects of combining trials with and without additional treatments in the analysis of antivirals verus placebo and the impact of length of follow up on the meta-analysis results.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Five randomized controlled trials with 1787 participants in total were added to the previous version of this review which had two trials and 200 participants. All five trials provided a comparison of disease outcome after antiviral treatment with disease outcome after an otherwise identical treatment regimen lacking the antiviral component. One thousand nine hundred and eighty-seven participants were included in the seven included studies.

Engstrom (Engström 2008) recruited 829 participants to be treated within 72 hours of onset and randomized by a computerised mechanism in a two-stage process into four treatment groups: valaciclovir with prednisolone or valaciclovir with placebo or placebo with prednisolone or double placebo in a factorial design. The trial was blinded for administrator, patient and assessment of recovery status until the end of follow-up. Participants were assessed at onset, after two weeks (11 to 17 days), after one, two, three, six and 12 months. Disease status was measured using the House-Brackmann grading system and the Sunnybrook scale. Recovery status was defined by a Sunnybrook score of 100 and a House-Brackman grade of 1. Time to recovery was estimated. Data analysis included an assessment of treatment interaction.

The study reported no effect on recovery time due to valaciclovir ($P = 0.76$). Recovery rates at 12 months were 57.5% in the valaciclovir group compared with 57.3% in the placebo group ($P = 1.00$). For this review, we aggregated the antiviral plus corticosteroid with the antiviral plus placebo group and the corticosteroid plus placebo with the double placebo group to achieve the most powerful comparison for the effect of treatment with valaciclovir on recovery rates at 12 months. We analysed these recovery rates 12 months after palsy onset from their results. With complete recovery defined as a Sunnybrook score of 100, 271 out of 413 recovered with valaciclovir compared with 266 out of 416 recovered without valaciclovir, RR 1.03. With complete recovery defined as a House-Brackmann grade of I, 297 out of 413 recovered with valaciclovir compared with 293 out of 416 without valaciclovir, RR 1.02.

Hato (Hato 2007) randomized 296 participants within seven days of onset using sealed envelopes into two treatment groups: valaciclovir with prednisolone or placebo with prednisolone. Two hundred and twenty-one participants were included in the final anal-

ysis. The administrators were not blinded to the treatment allocation but the participants were blinded to treatment received. Those assessing recovery status were not blinded to treatment. Participants' disease severity was assessed using the Yanagihara scale and were assessed as completely recovered if attaining a score greater than 36. Participants were assessed at onset and monthly thereafter for six months or until completely recovered if recovery occurred before six months.

The group reported significant benefit from treatment with antivirals and corticosteroids compared to corticosteroids alone: recovery in the group receiving valaciclovir and prednisolone was seen in 110/114 and recovery in the placebo and prednisolone group was seen in 96/107, RR 1.08 at six months after palsy onset.

Kawaguchi (Kawaguchi 2007) recruited 150 participants to be treated within seven days of onset and randomized using sealed envelopes into two treatment groups: valaciclovir with prednisolone or prednisolone alone. Thus we deduce that there was no blinding for administrator or participant. Participants were assessed at onset using both the Yanagihara 40-point scale and House-Brackmann index. Recovery was measured using only the Yanagihara index (36 or more). Recovery time in days was recorded. Follow up was scheduled for one week, two weeks and one, two, three, four, five and six months.

This trial reported no significant difference in recovery rate between the prednisolone group and the prednisolone-aciclovir group at six months.

Sullivan (Sullivan 2007) recruited 551 participants to be treated within 72 hours of onset and randomized by a dedicated remote telephone-computerised mechanism in a two-stage process into four treatment groups: aciclovir with prednisolone (AS) or aciclovir with placebo (AO) or placebo with prednisolone (OS) or double placebo (OO) in a factorial design. The trial was blinded for administrator, participant and assessment of recovery status until the end of follow-up. Participants were assessed at onset, after three months, and if still unwell at three months, after nine months. Recovery status was measured using the House-Brackmann scale with complete recovery defined by House-Brackmann grade I. Data analysis included an assessment of treatment interaction.

Sullivan (Sullivan 2007) reported final outcomes on 496 completed participants at three months and nine months and shows a beneficial effect of not receiving antivirals. The nine month recovery rates were 211 out of 247 in the aciclovir group compared with 226 out of 249 among participants not receiving aciclovir, RR 0.92.

Yeo (Yeo 2008) recruited 91 participants with Bell's palsy who were randomized to receive either aciclovir and prednisolone or prednisolone alone. All participants also received physical therapy and plasma volume expanders as adjuncts. The trial was double blind and participants were followed up for six months or until complete recovery. Recovery was assessed using the House-Brackmann scale and defined as a House-Brackmann score of 2 or less.

Yeo (Yeo 2008) reported outcomes for 91 participants at two and six months. There was no significant difference in recovery between the two treatment groups. The six month recovery rate in the antivirals and corticosteroids group was 44 out of 44 and in the corticosteroids only group 40 out of 47, RR 1.17.

Details of other studies previously included in this review are given below.

Adour (Adour 1996) recruited 119 participants of whom 99 were included in the published analysis. The study was double-blind and placebo-controlled. Participants were recruited within three or less days since the onset of paralysis and received either aciclovir and prednisolone or placebo and prednisolone. The study duration was four months and participants were reviewed at two weeks, two months and four months. This was a single centre study. The Facial Paralysis Recovery Index (FPRI) was used to measure facial function and the primary trial outcome was incomplete recovery defined by a FPRI 7 or less.

This study reported significant benefit of treatment with aciclovir plus corticosteroids compared with corticosteroids alone, RR 1.22 after four months.

De Diego (De Diego 1998) recruited 113 participants and included 101 in the final analyses. Participants were randomly assigned treatment: blinding status was not clear. Evaluation was carried out within 48 hours of the onset of symptoms and participants received either aciclovir for 10 days or prednisolone for 16 days (reducing dose). Reviews were scheduled for one, three, six and 12 weeks after initial contact with further contact if persistent incomplete recovery was noted. The primary study outcome was recovery as defined using the House-Brackmann and facial paralysis recovery profile scales. Full recovery was defined as a House-Brackman score of 2 or less or a Facial Paralysis Recovery Profile (FPRP) of 8 or more. The final length of follow-up is not reported but stated as 'until complete recovery or stabilization of the paralysis'.

This study reported significant treatment benefit in the corticosteroids only group, RR 0.83.

We have changed the status of the Antunes (Antunes 2000) study for this report from 'included' to 'excluded'. The authors of the previous edition of this review initially included it but found the data to be incomplete and, despite attempting to contact the authors, there was not sufficient information for the data to be usefully included in the analyses.

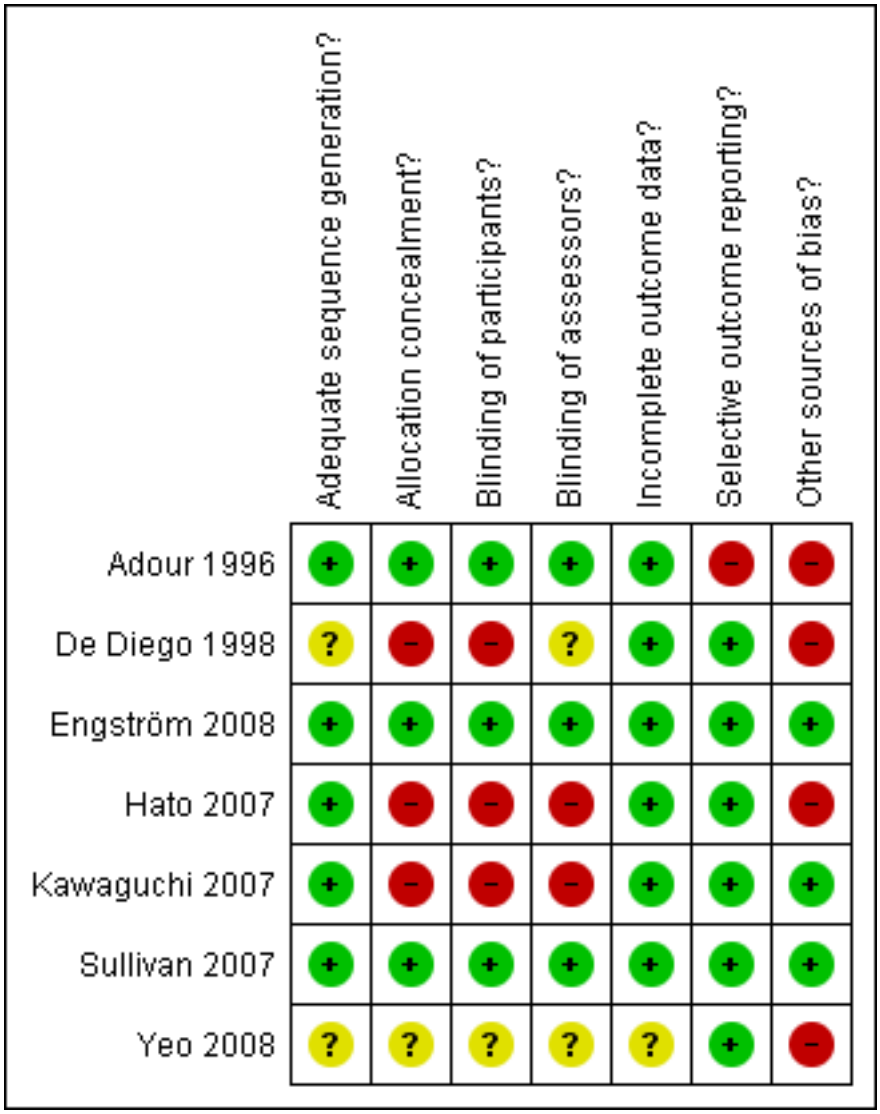
We have reassessed the inclusion of the two studies awaiting assessment (P de Aquino 2001; Roy 2005). The author of the previous version of this review, Dr. D. Allen, tried to contact the author of the former paper for clarification of the data, but this has not been forthcoming and so we have excluded this trial because of a lack of adequate information. The latter study appeared as an abstract in a journal supplement and has not, according to the search strategies employed, been published as a full paper. Again, this trial has been excluded due to a lack of adequate information. A further study awaits classification (Inanli 2001).This was in-

cluded in a recently published systematic review and meta-analysis (Goudakos 2009). We await translation and interpretation. Updated status of this paper will be included in the next update of the Cochrane Review.

Risk of bias in included studies

The risk of bias is summarised in Figure 1.

Figure 1. Risk of bias summary: review authors' judgments about each risk of bias domain for each included study.



Sequence generation, allocation concealment and blinding

Three studies (Adour 1996; Engström 2008; Sullivan 2007) were randomized, double-blind and placebo-controlled to minimise the effects of bias. Kawaguchi (Kawaguchi 2007) described a randomized study but states that the treatment was revealed to the clinician and the absence of a placebo made treatment clear to the recipient. The remaining two studies (De Diego 1998; Hato 2007) all described randomization but not blinding or placebo use. Yeo (Yeo 2008) stated that their study was randomized and double-blind: this was not described within the text and so this study has been graded as unclear for these attributes.

Incomplete outcome data

All studies, except Yeo (Yeo 2008) reported frequencies, and often reasons, for failure to complete follow-up.
Most trials (Engström 2008; Kawaguchi 2007; De Diego 1998; Sullivan 2007; Yeo 2008) reported a drop-out rate of 10% or less except Adour 1996,16.8% and Hato 2007,19% .

Selective outcome reporting

All studies, except Adour 1996 reported all their intended primary outcomes. Adour failed to report on audiometry and stapedial reflex testing. Engström 2008 reported all primary outcomes and stated that secondary outcomes will be reported in a later paper.

Other potential sources of bias

Diagnostic criteria

Six studies (De Diego 1998; Engström 2008; Hato 2007; Kawaguchi 2007; Sullivan 2007; Yeo 2008) gave adequate information. All studies explicitly mentioned a diagnosis of Bell's palsy and stated that other causes of facial palsy had been considered and excluded. Two trials (Hato 2007; Kawaguchi 2007) retrospectively excluded participants on the basis of positive serology for herpes simplex (HSV) or varicella zoster (VZV) viruses. Two studies (Engström 2008; Sullivan 2007) mention referral to specialists for diagnostic confirmation.
The remaining study Adour 1996 stated participants were diagnosed with Bell's palsy but did not give any further information.

Outcome criteria

All studies used referenced facial function scoring systems to grade recovery from facial paralysis. Adour (Adour 1996) used the Facial Paralysis Recovery Profile (FPRP) and the Facial Paralysis Recovery Index (FPRI). (Adour 1971). Hato (Hato 2007) and Kawaguchi (Kawaguchi 2007) used the Yanagihara scoring system (Yanagihara 2003), which has a validated system for conversion to the House-Brackmann scale (House 1985). De Diego (De Diego 1998) presented results using the FPRP and House-Brackmann scale (House 1985). Engstrom, Sullivan and Yeo (Engström 2008; Sullivan 2007; Yeo 2008) presented results using the House-Brackmann scale (House 1985) and Engstrom supplemented this using the Sunnybrook scale (Ross 1996) to minimise the effects of inter-rater variability.

Statistical analysis

Six out of the seven studies analysed gave adequate detail: they clearly stated and then used appropriate statistical tests. Only Hato (Hato 2007) scored unclear in this category as the tests used were not stated.

Differences in baseline between groups

Six out of the seven trials were adequate in this category. De Diego (De Diego 1998) found a significant difference in rates of hypertension between the two groups: further analysis revealed that there was no significant difference in trial outcomes as a result. Kawaguchi (Kawaguchi 2007) reported a significant difference between mean age of the treatment groups but further analysis of the age distribution using the Chi^2 test revealed no significant difference. In the tables in the other studies, no significant differences between the baseline groups were reported.

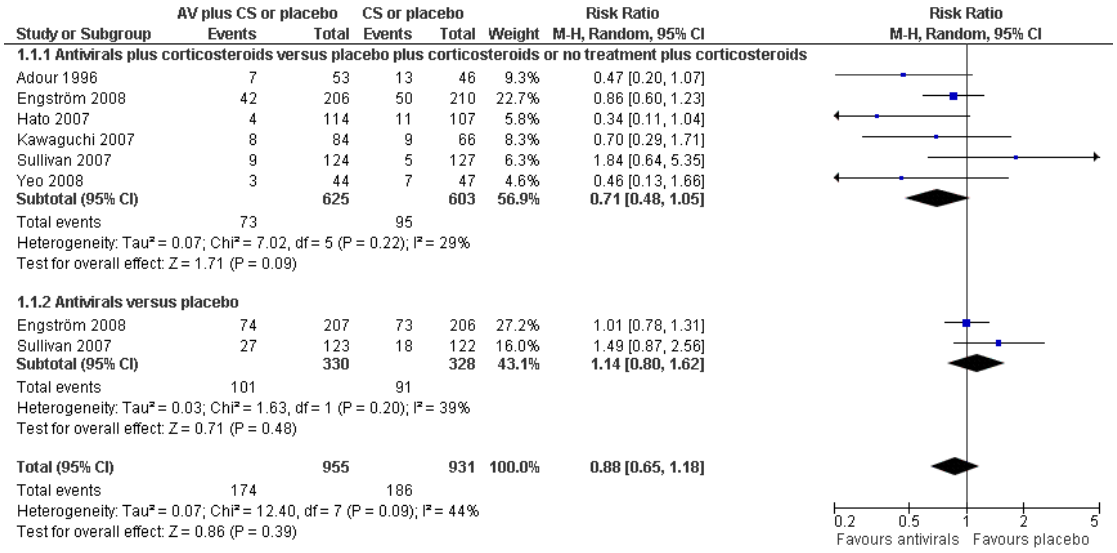
Effects of interventions

As all trials reported different intervals and lengths of follow up lengths, the analyses were performed on data reported at the end of the study periods of three months (De Diego 1998), four months (Adour 1996), six months (Hato 2007; Kawaguchi 2007; Yeo 2008) nine months (Sullivan 2007) or 12 months (Engström 2008) after the start of treatment.

Antivirals versus placebo (including antivirals plus corticosteroids versus placebo plus corticosteroids and antivirals plus corticosteroids versus no treatment plus corticosteroids)

This comparison contained six studies (Adour 1996; Engström 2008; Hato 2007; Kawaguchi 2007; Sullivan 2007 and Yeo 2008) with 1886 participants in total.
The relative rate of incomplete recovery at the end of the study did not show a significant difference between treatment with antiviral and treatment with placebo, the RR of incomplete recovery being 0.88 (95% CI 0.65 to 1.18), Analysis 1.1 and Figure 2. Heterogeneity was high when the fixed-effect model was used (Chi^2 = 11.78, P 0.04, I^2 58%), the random-effects model was used to partially correct for this.

Figure 2. Forest plot of comparison: 1 Antivirals versus placebo or no treatment including comparisons in which corticosteroids were given to both groups, outcome: 1.1 Incomplete recovery at end of study.



We analysed two subgroups of these trials.Two trials (Engström 2008 and Sullivan 2007) provided data for both these comparisons. For the six trials with altogether 1228 participants, which compared antivirals plus corticosteroids with corticosteroids plus placebo or no treatment, (Adour 1996; Engström 2008; Hato 2007; Kawaguchi 2007; Sullivan 2007 and Yeo 2008), there was a significant but slight reduction in the rate of incomplete recovery, RR 0.64 (0.50 to 0.82), favouring the combination of antivirals and corticosteroids over corticosteroids alone. For two trials (Engström 2008 and Sullivan 2007) which compared antivirals with placebo without any complicating additional treatment, there were 658 participants and the relative rate of incomplete recovery was again non-significant, RR 1.14 (95% CI 0.80 to 1.62).

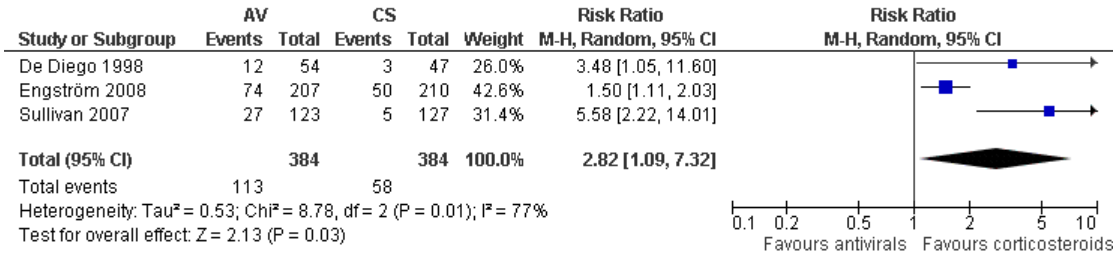
One study comparing antivirals and corticosteroids with corticosteroids alone (Adour 1996) had data for the outcome motor synkinesis or crocodile tears at the end of the study, Analysis 1.2. This included 99 participants and showed no significant difference between antivirals and corticosteroids, RR 0.47 (95% CI 0.20 to 1.07)

Adverse events were slightly, but not significantly, less likely with antiviral treatment than without, Analysis 1.3, RR 1.06 (95% CI 0.81 to 1.38). This analysis included data from three studies (Engström 2008; Hato 2007 and Sullivan 2007) and 1544 participants.

Antivirals versus corticosteroids

This comparison contained three studies (De Diego 1998; Engström 2008 and Sullivan 2007) with 768 participants in total. All three studies gave data for our primary outcome, recovery at the end of the study. Incomplete recovery was significantly less common in the participants treated with antivirals than those treated with corticosteroids. Initial calculations using the fixed-effect model showed RR 1.96 (95% CI 1.48 to 2.59) but with a high degree of heterogeneity (Chi^2 8.78, P = 0.01, I^2 77%). The analysis was repeated using the random-effects model to partially correct for this, Analysis 2.1 and Figure 3 , RR 2.82 (95% CI 1.09 to 7.32).

Figure 3. Forest plot of comparison: 2 Antivirals versus corticosteroids, outcome: 2.1 Incomplete recovery at end of study.



De Diego (De Diego 1998) alone reported motor synkinesis or crocodile tears at the end of the study. This analysis contains data on 101 participants and showed no significant difference between antiviral and corticosteroid, the RR being only 1.03 (95% CI 0.51 to 2.07), Analysis 2.2, .

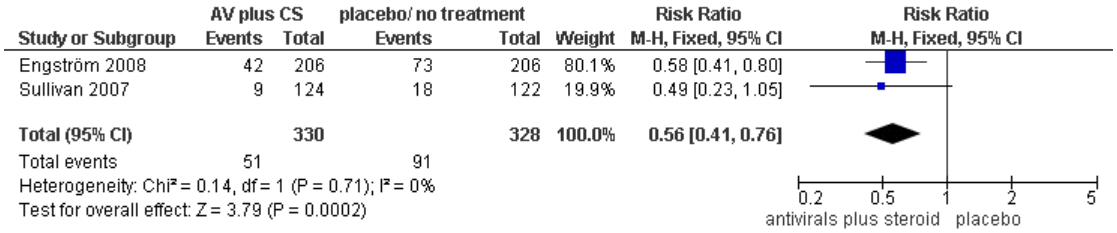
Adverse event data were available from the Sullivan 2007 and Engström 2008 trials. There was no significant difference between the groups, with RR 0.96 (95% CI 0.65 to 1.41) fewer participants with adverse events in the antivirals than the placebo groups, Analysis 2.3.

Antivirals plus corticosteroids versus placebo

This comparison contained two studies (Engström 2008; Sullivan 2007) and outcome data on 658 participants.

Incomplete recovery at the end of the study was significantly much less common with the combined treatment than placebo, Analysis 3.1 and Figure 4, RR 0.56 (95% CI 0.41, 0.76). This analysis had low heterogeneity (Chi^2 0.14, P 0.71, I^2 0%).

Figure 4. Forest plot of comparison: 3 Antivirals and corticosteroids versus placebo, outcome: 3.1 Incomplete recovery at end of study.



There were no data available for motor synkinesis or crocodile tears at the end of the studies.

Adverse events were slightly but not significantly more common with combined treatment than with placebo, RR 1.15 (95% CI 0.79 to 1.66), Analysis 3.2.

Sensitivity analyses

We investigated the effects of using the comparison antivirals plus corticosteroids, placebo or no treatment versus corticosteroids, placebo or no treatment by performing further analyses to investigate whether our conclusions were altered when studies with a follow-up of less than six months were excluded (De Diego 1998 and Adour 1996) and when only outcomes reported at greater than six months were included (Engström 2008 and Sullivan 2007).

Further sensitivity analysis was performed to assess the potential difference in participant response to aciclovir (Adour 1996, De Diego 1998, Kawaguchi 2007, Sullivan 2007 and Yeo 2008) versus valaciclovir (Engström 2008 and Hato 2007).

Antivirals versus placebo (including antivirals plus corticosteroids versus placebo or no treatment plus corticosteroids)

When Adour 1996 was excluded, the RR of incomplete recovery was 0.94 (95% CI 0.71 to 1.26, n = 1787). When Adour 1996; Hato 2007; Kawaguchi 2007 and Yeo 2008 were excluded, the RR of incomplete recovery was 1.06 (95% CI 0.83 to 1.35, n = 1325). This represents no significant change seen with the removal of outcomes which reported follow up at six months or less.

When sensitivity analysis was performed to assess the differing response to aciclovir and valaciclovir, no significant difference was found. Overall the RR for aciclovir was 0.93 (95% CI 0.45 to 1.90, n = 686) in an analysis which included data from three trials. Overall the RR for valaciclovir was 0.87 (95% CI 0.66 to 1.14, n = 1200) in an analysis including data from three trials.

Antivirals versus corticosteroids

When the De Diego 1998 study was excluded and the analysis was just performed with Engström 2008 and Sullivan 2007, the relative risk of more benefit with antivirals than with corticosteroids, for the outcome incomplete recovery at the end of the study, was no longer significant, RR 2.69 (95% CI 0.73 to 10.01, n = 667).This study differed in reporting outcome at less than six months and its exclusion changed the conclusion of the meta-analysis from "significant" to "non-significant".

Sensitivity analysis assessing the differing response to aciclovir versus valaciclovir did not alter the overall conclusion from the meta-analysis. The respective results were RR aciclovir 4.68 (95% CI 2.25 to 9.74, n = 351) with data from two trials and valaciclovir RR 1.50 (95% CI 1.11 to 2.03, n = 417) with data from one trial.

Antiviral plus corticosteroid versus placebo

There was no change in the data for this analysis, based on Engström 2008 and Sullivan 2007. This represents no significant effect from excluding studies, which report the outcome incomplete recovery at the end of the study, which report at less than 6 months.

Sensitivity analysis looking at aciclovir and valaciclovir both resulted in a change to these results. For aciclovir, with data from one trial, the RR was 0.49 (95% CI 0.23 to 1.05, n = 246) and for valaciclovir, again with data from one trial, the RR was 0.58 (95% CI 0.41 to 0.80, n = 412). In both cases, this represents a loss of significance in the difference between outcomes for antivirals plus corticosteroids versus placebo.

DISCUSSION

This updated review resolves much of the uncertainty about the value of herpes simplex antivirals for Bell's palsy. There was no evidence of significant benefit from antivirals in comparison with placebo but they were significantly less efficacious than corticosteroids.

When antivirals were compared to placebo, there was little difference in the recovery of participants receiving either treatment RR 0.88 (95% CI 0.65 to 1.18). This result was influenced by the Sullivan 2007 trial which suggested that antiviral treatment had a non-significant detrimental effect on recovery: 27 out of 123 participants receiving antivirals had incomplete recovery compared to 18 out of 122 participants receiving placebo, RR 1.48 (95% CI 0.87 to 2.56). A possible reason is that, although active against the presumed infective agent, antiviral medication causes increased local inflammation and exacerbation of symptoms (Jarisch-Herxheimer reaction).

When antiviral treatment was compared to corticosteroid treatment, the participants receiving corticosteroid treatment were significantly more likely to recover than those receiving antiviral treatment: that is, there was more incomplete recovery in the antiviral group RR 2.82 (95%CI 1.09 to 7.32). This analysis displayed significant heterogeneity which was not fully corrected by applying the random-effects model and needs to be interpreted with caution.

Similarly, the outcome was significantly better in the participants receiving corticosteroid and antiviral treatment compared with placebo: that is the RR of incomplete recovery was significantly less, 0.56 (95% CI 0.41 to 0.76), in those who received combined treatment.

The RR of incomplete recovery, calculated using the fixed-effects model, was significantly less 0.75 (95% CI 0.57 to 0.98) with the combined treatment than with corticosteroids alone which would suggest a beneficial effect from antivirals but this analysis showed moderate heterogeneity and should be interpreted with caution.

The source of heterogeneity may be due to clinical variation for example in study participant characteristics, disease severity at baseline, delay in receiving treatment or type of antiviral agent used. Equally, variation may be due to methodological considerations such as method of randomization, the use of blinding, the choice of outcome assessment measures and recovery cut-off points or the trial duration. In particular, Hato 2007 and Kawaguchi 2007 had methodological weaknesses in baseline group assessment, completeness of follow-up and adequate blinding. Any of these factors could result in bias and introduce inaccuracy.The heterogeneity was exacerbated by keeping the inclusion criteria fairly broad: this maximises data inclusion and therefore power, but results must be interpreted with this in mind.

Sensitivity analysis of trials with data with less than a six month end-point showed results similar to those achieved with the whole group analysis - no significant effect of shortened time of follow up was detected.

Similarly, sub-group analysis of the relative treatment difference with different antivirals showed no significant change in the antivirals versus placebo or antivirals versus corticosteroids results.

In the antivirals plus corticosteroids comparison, the examination of individual therapy removed the significant difference in incomplete outcome. Given this, it is unlikely that different antivirals, despite the difference in bio-availability (Sullivan 2007), will have a significant affect on the outcome of incomplete recovery at the end of the study.

Given that a significant benefit in terms of incomplete recovery at end of study was derived from the combination of antivirals plus corticosteroids, this may merit further investigation. It may be that the use of prednisolone suppresses the Jarish-Harxheimer reaction and allows the antiviral treatment to provide some benefit.

There were insufficient data to examine any other variables which are reported in the studies, such as pain, quality of life and variation in response due to time to treatment and severity at onset. These variables can be used as hypothesis generation for future work in this area.

From the minimal data available for comparison of motor synkinesis or crocodile tears at the end of the study, the results of two studies with separate comparisons with a total number of participants of 200 were not significant. De Diego (De Diego 1998) compared antivirals with corticosteroids and found fewer episodes of these outcomes in the corticosteroids group while Adour (Adour 1996) compared antivirals and corticosteroids with corticosteroids and found fewer episodes of these outcomes in the antiviral treatment group. Relatively low participant numbers and a degree of clinical (different clinical assessment scales used) and methodological heterogeneity (different treatment regimes and follow up plans) limit the interpretation of these data.

No data were available in any of the studies to assess the outcome 'complete paralysis at the end of the study'.

Adverse events data were available in three studies (Engström 2008; Hato 2007 and Sullivan 2007) giving comparison data on 1544 participants. None of the comparisons showed significant differences in adverse events between either arm . No correlation with specific treatment could be found within these results.

There has been variation in the clinical end-points chosen as defining recovery: Engstrom and Sullivan (Engström 2008; Sullivan 2007) use House-Brackmann (H-B) Grade 1: Yeo used H-B Grade 2. The other studies used a variety of different scales which show more or less equivalence to these. Additional information is attached which give details of the symptoms scales and comparison where available (Table 1; Table 2; Table 3)

Age at onset, either as an independent predictor of recovery or as a predictor or treatment response might be an important variable: Kawaguchi (Kawaguchi 2007) stratified for age and noted a significantly lower recovery rate in 40 to 60 year olds compared to those under 40 years old.

Neither Kawaguchi (Kawaguchi 2007) nor Yeo (Yeo 2008) found a significant association between time to treatment and final recovery status.

There were differences in severity at recruitment: several studies were based in secondary care (Hato 2007; Kawaguchi 2007 and Yeo 2008) and so may have included a more severe spectrum of palsy than those based within primary care. Hato and Kawaguchi (Hato 2007; Kawaguchi 2007) stratified by severity of disease status at onset and found that in cases of complete or severe palsy the recovery rate for the combination treatment was significantly greater than that for the corticosteroid only group.

Studies conducted in Asia, North America and Europe, have been included. It is possible that genetic differences in drug metabolism or response or even different aetiological processes may account some of the variation in response which is observed.

The other important consideration which is raised by the primary outcome result are the health economic issues: a 10 day course of aciclovir 400 mg five times daily costs GBP 9.28; valaciclovir and famciclovir equivalent courses cost significantly more; a 10 day course of prednisolone (two 25 mg tablets daily), costs about GBP 7.14 (BNF 2008). These cost data are specific to the current UK market and costs vary significantly in other countries (Hernández 2008).

Further work in this area could address the questions raised by the possible causes of heterogeneity in some of the comparisons in this review and may be achieved through a combination of epidemiological work and further large randomized controlled trials which collect comparable data for sub-group analysis and meta-regression.

AUTHORS' CONCLUSIONS

Implications for practice

High quality evidence from randomized controlled trials of herpes simplex antivirals for the treatment of Bell's palsy showed no significant benefit from antivirals compared to placebo. High quality evidence showed significant benefit from the combination of antivirals and corticosteroids compared with placebo. Moderate quality evidence showed significantly less benefit from antivirals than corticosteroids. There was no significant increase in adverse events from antivirals compared with either placebo or corticosteroids.

Implications for research

The results cast doubt on previous hypotheses suggesting herpes simplex as the cause of Bell's palsy and research should be aimed at discovering alternative causes.

More work is needed to assess the likelihood of long term cosmetic sequelae. Sub-group analysis of existing data and future studies

should be done to assess the impact of variables such as time from diagnosis until treatment received, severity of palsy at baseline and age of patient at presentation on the outcome. Work assessing softer end-points such as quality of life and perceived disability should be done to develop better understanding of Bell's palsy at the patient level.

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REFERENCES

References to studies included in this review

Adour 1996 *{published data only}*

* Adour KK, Ruboyianes JM, Von Doersten PG, Byl FM, Trent CS, Quesenberry CP, et al.Bell's palsy treatment with acyclovir and prednisone compared with prednisone alone: a double-blind, randomised, controlled trial. *Annals of Otology, Rhinology and Laryngology* 1996;**105**(5):371–8.

De Diego 1998 *{published data only}*

* De Diego JI, Prim MP, De Sarria MJ, Madero R, Gavilan J. Idiopathic facial paralysis: A randomised, prospective and controlled study using single-dose prednisone versus acyclovir three times daily. *Laryngoscope* 1998;**108**(4 pt 1): 573–5.

Engström 2008 *{published data only}*

* Engström M, Berg T, Stjernquist-Desatnik A, Axelsson S, Pitkäranta A, Hultkrantz M, et al.Prednisolone and valaciclovir in Bells Palsy: a randomised, double blind, placebo controlled, multi-centre trial. *The Lancet* 2008;**7** (11):993–1000. [DOI: 10.1016/51474-4422(08)70221-7]

Hato 2007 *{published data only}*

* Hato N, Yamada H, Kohno H, Matsumoto S, Honda N, Gyo K, Fukuda S, et al.Valaciclovir and Prednisolone Treatment for Bell's Palsy: A Multicenter, Randomized, Placebo-Controlled Study. *Otology and Neurotology* 2007; **28**:408–13.

Kawaguchi 2007 *{published and unpublished data}*

* Kawaguchi K, Inamura H, Abe Y, Koshu H, Takashita E, Muraki Y, et al.Reactivation of Herpes Simplex Virus Type 1 and Varicella-Zoster Virus and Therapeutic Effects of Combination Therapy with Prednisolone and Valacyclovir in Patients with Bells Palsy. *The Laryngoscope* 2007;**117**(1):147–56. [DOI: 10.1%60097/ 01.mlg.0000248737.65607.9e]

Sullivan 2007 *{published and unpublished data}*

* Sullivan FM, Swan IRC, Donnan PT, Morrison JM, Smith BH, McKinstry B, et al.Early Treatment with Prednisolone or Acyclovir in Bell's Palsy. *The New England Journal of Medicine* 2007;**357**(16):1598–607.

Yeo 2008 *{published data only}*

Yeo SG, Lee YC, Park DC, Cha CI. Aciclovir and steroid versus steroid alone in the treatment of Bell's Palsy. *American Journal of Otolaryngology - Head and Neck Medicine and Surgery* 2008;**29**(3):163–68.

References to studies excluded from this review

Ahangar 2006 *{published data only}*

* Ahangar AA, Hosseini S, Saghebi R. Comparison of the efficacy of prednisolone versus prednisolone and acyclovir in the treatment of Bell's Palsy. *Neurosciences* 2006;**11**(4): 256–59.

Antunes 2000 *{published data only (unpublished sought but not used)}*

Antunes ML, Fukuda Y, Testa JRG. Clinical treatment of Bell's palsy: comparative study among valaciclovir plus deflazacort, deflazacort and placebo. *Acta AWHO* 2000;**19**: 68–75.

Axelsson 2003 *{published data only}*

* Axelsson S, Lindberg S, Stjernquist-Desatnik A. Outcome of Treatment with Valacyclovir and Prednisone in Patients with Bell's Palsy. *Annals of Otology, Rhinology and Laryngology* 2003;**112**(3):197–201.

Chen 2005 *{published data only}*

Chen Liangwei, Yang Zhaohui, Huang Zhiquan. Outcome of treatment of 46 patients with Bell's Palsy with aciclovir and prednisolone. *Shanghai Journal of Stomatology* 2005;**14** (6):590–92.

Hato 2003 *{published data only}*

* Hato N, Matsumoto S, Kisaki H, Takahashi H, Wakisaka H, Honda N, Gyo K, Murakami S, Yanagihara N. Efficacy of Early Treatment of Bells Palsy with Oral Acyclovir and Prednisolone. *Otology and Neurotology* 2003;**24**(6):948–51.

Hultcrantz 2005 *{published data only}*

* Hultcranzt M. Treatment of facial paralysis - evidence-based recommendations. *Lakartidningen* 2005;**102**(10): 744–75.

Ibarrondo 1999 *{published data only}*

* Ibarrondo J, Navarrete ML, Encarnacion LF, Quesada P, Crespo F, Carcia M, et al.Treatment of idiopathic facial paralysis: corticoids versus acyclovir versus empirical treatment [Tratamiento de la paralisis facial idiopatica: corticoides versus aciclovir versus empirico]. *Acta Otorrinolaringologica Espanola* 1999;**50**(2):118–20. [MEDLINE: 1999238351]

P de Aquino 2001 ***{published data only (unpublished sought but not used)}***

* de Aquino P, J Evandro P, Filho C, Alvares N. Comparative Study of three types of treatment of idiopathic facial palsy (Bell) [Estudo comparativo com tres tipos de tratamento clinico na paralisa facial idiopatica (Bell)]. *Acta AWHO* 2001;**20**(4):195–200.

Ramos Macias 1992 ***{published data only}***

* Ramos Macias A, De Miguel Martinez I, Martin Sanchez AM, Gomez Gonzalez JL, Martin Galan A. Incorporation of acyclovir in the treatment of peripheral paralysis. A study of 45 cases [Incorporacion del aciclovir en el traitemento de la paralisis periferica. Un estdio en 45 casos]. *Acta Otorrinolaringologica Espanola* 1992;**43**(2):117–20. [MEDLINE: 1992297334]

Roy 2005 ***{published data only}***

Roy A, Jose J, Kamath V, Matthew T. Efficacy of aciclovir and methylprednisolone versus methylprednisolone alone in the treatment of Bell's palsy. *Journal of the Neurological Sciences* 2005;**238**(Suppl 1):S207.

Zhou 1999 ***{published data only}***

* Zhou P. Aciclovir in treating Bell's palsy. *Chinese Journal of New Drugs and Clinical Remedies* 1999;**18**:13–4.

References to studies awaiting assessment

Inanli 2001 ***{published data only}***

Inanli S, Tutkun A Ozturk O, et al.Idiopathic facial nerve paralysis treatment with aciclovir and prednisolone alone. *Turkish Archives of Otology* 2000;**39**:19–24.

Additional references

Abiko 2002

Abiko Y, Ikeda M, Hondo R. Secretion and dynamics of herpes simplex virus in tears and saliva of patients with Bell's Palsy. *Otology and Neurology* 2002;**23**:779–83.

Adour 1971

Adour KK Swanson PJ Jr. Facial paralysis in 403 consecutive patients: emphasis on treatment response in patients with Bell's palsy. *Transactions - American Academy of Opthalmology and Otolarygnology* 1971;**75**:1284–1301. [MEDLINE: 1972258401]

Allen 2007

Allen D, Dunn L. Aciclovir or valaciclovir for Bell's Palsy (idiopathic facial palsy). *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD001869.pub2.]

Bateman 1992

Bateman DE. Facial Palsy. *British Journal of Hospital Medicine* 1992;**47**:430–31.

BNF 2008

British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary*. 6th Edition. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2008.

Brandenberg 1993

Brandenberg NA, Annegers JF. Incidence and risk factors for Bell's Palsy in Laredo, Texas. *Neuroepidemiology* 1993; **12**(6):313–25. [MEDLINE: 1994142820]

Egger 2007

Egger M, Davey Smith G, Altman DG. *Systematic Reviews in Health Care: Meta-Analysis in Context*. 6th Edition. BMJ Books, 2007. [ISBN: 978–0–7279–1488–0]

Goudakos 2009

Goudakos JK, Markou KD. Corticosteroids versus corticosteroids plus antiviral agents in the treatment of Bell Palsy. *Archives of Otolaryngology, Head and Neck Surgery* 2009;**135**(6):558–64.

Hernández 2008

Hernández RA, Sullivan F, Donnan P, Swan I, Vale L. Economic evaluation of early administration of prednisolone and/ or aciclovir for the treatment of Bell's palsy. *Family Practice* 2009;**2**:137–44.

House 1985

House JW, Brackmann DE. Facial nerve grading system. *Otolarnygology - Head & Neck Surgery* 1985;**93**(2):146–7. [MEDLINE: 1985189410]

Katusic 1986

Katusic SK, Beard CM, Wiederholt WC, Bergstrahl EJ, Kurland LT. Incidence, clinical features and prognosis in Bell's Palsy. *Annals of Neurology* 1986;**20**(5):622–7. [MEDLINE: 1987074746]

May 1976

May M, Wette R, Hardin WB. The use of steroids in Bells palsy: a prospective controlled study. *Laryngoscope* 1976;**86**: 1111–2.

McCormick 1972

McCormick DP. Herpes simplex as a cause of Bell's Palsy. *Lancet* 1972;**1**(7757):939–39.

Morgan 1995

Morgan M, Moffat M, Ritchie L, Collacott I, Brown T. Is Bell's Palsy a reactivation of varicella zoster virus?. *Journal of Infection* 1995;**30**:29–36.

Morgenlander 1990

Morgenlander JC, Massey EW. Bell's Palsy: ensuring the best possible outcome. *Postgraduate Medicine* 1990;**88**(5): 157–62.

Murakami 1996

Murakami S, Mizobuchi M, Nakashiro Y, Doi T, Hato N, Yanagihara N. Bells Palsy and Herpes Simpex Virus: Identification of Viral DNA in Endoneurial Fluid and Muscle. *Annals of Internal Medicine* 1996;**124**:27–30.

Petruzelli 1991

Petruzelli GJ, Hirsch BE. Bell's Palsy. *Postgraduate Medicine* 1991;**90**:115–127.

Pietersen 1982

Pietersen E. The natural history of Bell's Palsy. *American Journal of Otoloaryngology* 1982;**4**:107–111. [MEDLINE: 1983072045]

Pietersen 2002
Pietersen E. Bell's Palsy: the spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies.. *Acta Oto-laryngologica Supplementum* 2002;**Suppl(549)**:4–30.

Ross 1996
Ross BG, Fradet G, Nedzelski JM. Development of a sensitive clinical facial grading system. *Otolargynology Head and Neck Surgery* 1985;**93**:146–7.

Rowlands 2002
Rowlands S, Hooper R, Hughes R, Burney P. The epidemiology and treatment of Bell's palsy in the UK. *European Journal of Neurology* 2002;**9**(1):63–7.

Salinas 2002
Salinas RA, Alvarez G, Alvarez MI, Ferreira J. Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane Database of Systematic Reviews* 2002, Issue 2.

Stjernquist-Desatnik 2006
Stjernquist-Desatnik A, Skoog E, Aurelius E. Detection of herpes simplex and varicellla-zoster viruses in patients with Bell's palsy by the polymerase chain reaction technique. *Annals Otology Rhinology Laryngology* 2006;**115**:306–311.

Sugita 1995
Sugita T, Murakami S, Yanagihara N, Fujiwara Y, Hirata Y, Kurata T. Facial nerve paralysis induced by herpes simplex virus in mice: an animal model of acute and transient facial paralysis. *Annals of Laryngology* 1995;**104**:574–81.

Takasu 1992
Takasu T, Furata Y, Sato KC, Fukada S, Inuyama Y, Nagashima K. Detection of latent herpes simplex virus DNA and RNA in human geniculate ganglia by the polymerase chain reaction. *Acta otolaryngologica* 1992;**112** (6):1004–11.

Theil 2001
Theil D, Arbusow V, Defuss T, Strupp M, Pfeiffer M, Mascolo A, Brandt T. Prevelance of HSV-1 LAT in human trigeminal, geniculate and vestibular ganglia and its implication for cranial nerve syndromes.. *Brain Pathology* 2001;**11**:408–13.

Wolf 1978
Wolf SM, Wagner JH, Davidson S, Forsythe A. Treatment of Bell's palsy with prednisone: a prospective randomised study. *Neurology* 1978;**28**(2):158–61.

Yanagihara 1988
Yanagihara N, Yumoto E, Shibahara T. Familial Bell's palsy: Analysis of 25 families. *Annals of otology, rhinology and laryngology* 1988;**137 suppl**:8–10.

Yanagihara 2003
Yanagihara N, Hato N. Assessment of facial nerve function following acoustic neuroma surgery: Facial nerve grading system. Acoustic Neuroma: consensus on systems for reporting results 2003; Vol. 10:91–98.

References to other published versions of this review

Allen 2007
Allen D, Dunn L. Aciclovir or valaciclovir for Bell's Palsy (idiopathic facial paralysis). *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD001869.pub2; : CD001869]

Sipe 2002
Sipe J, Dunn L. Aciclovir for Bell's palsy (idiopathic facial paralysis). *Cochrane Database of Systematic Reviews* 2002, Issue 2.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Adour 1996

Methods	Double-blind. Placebo-controlled.
Participants	119 randomized, 99 included in published analysis. Initial diagnosis of idiopathic facial paralysis in primary care clinics or emergency departments confirmed in facial paralysis research clinic. Enrolment criteria: paralysis commenced <= 3 days before treatment; all participants over 18 years of age; good physical health determined by history and physical exam; no contraindication for steroid or aciclovir treatment; all women of childbearing age had a negative pregnancy test result
Interventions	Aciclovir (2000 mg per day for 10 days) and prednisone (1 mg/kg for 5 days tapered to 10 mg/day for remaining 5 days) or placebo and prednisone (1 mg/kg for 5 days tapered to 10 mg/day for remaining 5 days)
Outcomes	Primary outcome: recovery on facial paralysis recovery index where incomplete recovery is Facial Paralysis Recovery Profile (FPRP) <=7 at 4 months Maximal stimulation test +/- electroneurogrpahy at follow up at 2 weeks, 2 months, 3 months and 4 months (if incompete recovery) after paralysis onset Final outcomes reported at 3 months or when recovered or palsy stabilized (not more clearly defined)
Notes	Single centre. Exclusion criteria: no other medication for idiopathic facial paralysis, urea nitrogen or creatinine > 2x upper limit of normal, liver transaminase > 3x upper limit of normal; haemoglobin level <100 g/L; platelet count < 75 000/mm3; or neutrophil count <1 x 10 to the 6/L

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote "the bottles [of aciclovir and placebo], provided by Burroughs Wellcome, were randomised in groups of 10"
Allocation concealment?	Yes	Quote "Each bottle..had a sealed identification label which was removed intact and kept with the patient's record"
Blinding of participants?	Yes	Quote "eligible patients were given identical, unlabeled bottles of 100 capsules that contained either palcebo or aciclovir (Zovirax), 200 mg" Patients in each group received identical follow-up
Blinding of assessors?	Yes	The study is reported as double blind: the method reported is consistent with being able to achieve this
Incomplete outcome data?	Yes	The numbers of participants unable to complete the study is given

Adour 1996 (*Continued*)

Selective outcome reporting?	No	Primary outcome of facial paralysis recovery profile and bilateral facial nerve electrical testing both reported but no data given on audiometry with stapedial reflex testing
Other sources of bias?	No	Single centre study High drop out rate reported - 16.8% Diagnostic criteria not clearly defined in paper

De Diego 1998

Methods	Participants randomly assigned. No further details given.
Participants	113 participants randomized, 101 included in published analysis. Evaluation within first 96 hours. No contraindications to corticosteroid or aciclovir
Interventions	Aciclovir (2400 mg per day for 10 days) or prednisone (1 mg/kg for 10 days then tapered to zero over next 6 days)
Outcomes	Primary outcome: recovery using House-Brackman facial nerve grading scale and facial paralysis recovery profile (FPRP) (Adour 1971). Where recovery was defined as H-B score <= 2 or FPRP >= 8. Denervation reported with maximal stimulation test and electromyography in severe cases. Sequelae and synkinesis recorded separately Follow up at 1, 3, 6, 12 weeks after first visit. Participants with incomplete recovery at 12 weeks followed until recovery made or stabilisation of paralysis Final outcomes reported at 4 months.
Notes	Single centre. Both House-Brackman and FPRP scales used.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote "Patients were randomly assigned".
Allocation concealment?	No	No clear information but unlikely to be true as no indication of blinding - see below
Blinding of participants?	No	Presence of blinding not clearly stated but unlikely to be the case as groups receive different treatment regimens (corticosteroids once daily or aciclovir three times daily) with no clear method for concealing this difference
Blinding of assessors?	Unclear	This is not mentioned in the study.
Incomplete outcome data?	Yes	Number lost to follow up reported.

De Diego 1998 (*Continued*)

Selective outcome reporting?	Yes	All desired outcomes reported.
Other sources of bias?	No	Single centre study.

Engström 2008

Methods	Participants randomized by computerised mechanism in a two-stage process into four treatment groups.: valaciclovir with prednisolone (AS), valaciclovir with placebo (AO), placebo with prednisolone (OS) or double placebo (OO)
Participants	829 participants randomized within 72 hours of facial palsy onset. No contraindications to corticosteroids or antivirals use
Interventions	Participants allocated into one of four treatment groups as described above and received a combination of valaciclovir 1000 mg three times daily for 7 days +/- prednisolone 60 mg daily for 5 days
Outcomes	Primary outcome: recovery of facial function, as assessed at all visits with the Sunnybrook Scale and the House-Brackmann Scale. Where complete recovery was taken as Sunnybrook scale 100 or H-B grade 1 Degree of pain as recorded during the first 2 months and adverse events were recorded for the first month. *Borrelia burgdorferi* serology was measured at baseline and 2 months. Frequency of severe pain, synkinesis, facial spasm and residual facial symptoms at 12 months is recorded Follow up at 2 weeks, 1 month, 2 months 3 months, 6 months and 12 months after randomization according to recovery Final outcomes reported at 12 months.
Notes	Multi-centre. Sunnybrook and House-Brackman scales used.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote "..randomization code was developed by Glaxo Wellcome GmBH, with a computer number generator to select random permuted blocks of eight"
Allocation concealment?	Yes	Randomization code double-blind and held by third party - medication dispensed in identical containers according to allocation concealment
Blinding of participants?	Yes	Study drugs issued in identical containers. All participants blinded to treatment group until study completion
Blinding of assessors?	Yes	All study personnel and data analysts blinded to treatment group until study completion

Engström 2008 (*Continued*)

Incomplete outcome data?	Yes	Numbers lost to follow up and reasons for this given.
Selective outcome reporting?	Yes	Secondary outcomes listed but not reported: all primary outcomes reported. Other outcomes will be reported in another paper due to space constrictions
Other sources of bias?	Yes	No other potential sources of bias identified.

Hato 2007

Methods	Random allocation to 2 groups to receive either valaciclovir and prednisolone (VP) or placebo and prednisolone (PP). Using the 'envelope' method
Participants	296 participants randomized; 152 participants to VP, 144 participants to PP. All participants commenced treatment within 7 days of onset of palsy. All participants over 15 years and had no contraindications to antivirals or corticosteroids. 221 patients were included in the final analysis
Interventions	Randomized to receive prednisolone 60 mg for 5 days, 30 mg for 3 days and 10 mg for 2 days +/- valaciclovir 1000 mg/ day for 5 days. All participants received mecobalamin 1500 micrograms per day following corticosteroids for 6 months or until complete recovery
Outcomes	Primary outcome full recovery based on a score of >= 36 on the Yanagihara scale Follow up at 1,3 and 6 months after commencing treatment. Final outcomes reported at 6 months.
Notes	Multi-centre: 6 academic tertiary referral centres. Measurements using Yanagihara scale - conversion scale to House-Brackmann scale included in paper

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote "the patients were randomly divided into two groups using the envelope method"
Allocation concealment?	No	Allocation was only concealed until intervention assigned.
Blinding of participants?	No	Inadequate. Participants blinded to treatment but different treatments with different frequencies mean true blinding was not achieved
Blinding of assessors?	No	Inadequate - not done. Assessors not blinded to treatment.

Hato 2007 (*Continued*)

Incomplete outcome data?	Yes	Participants who did not complete the study have frequency and reason for drop out documented
Selective outcome reporting?	Yes	Main outcome measures all reported.
Other sources of bias?	No	High drop out rate reported - 19%. Statistical tests employed not clearly stated.

Kawaguchi 2007

Methods	Random allocation to receive either prednisolone or prednisolone and valaciclovir. Using the 'envelope' method
Participants	150 participants: 66 prednisolone, 84 prednisolone and valaciclovir. All participants received treatment within 7 days from onset of palsy. All participants aged 15 or older and had no contraindications to corticosteroids or antivirals
Interventions	Participants received 20 mg three times daily for days 1 to 5, then 10 mg three times daily days 6 to 8, then 10 mg daily days 9 and 10 +/- valaciclovir 500 mg twice a day for 5 days
Outcomes	Facial movement and recovery measured using the Yanagihara scale where compete recovery was taken as a score of >= 36 Virological examination for presence of antiHSV and VZV antibodies and detection of HSV and VZV reactivation. Frequency of incomplete recovery at end of study and adverse events recorded but not published - information obtained from author (by PL) Follow up for 6 months at 1 and 2 weeks after treatment and then at 1, 2, 3, 4, 5 and 6 months after treatment Final outcomes reported at 6 months.
Notes	Multi-centre: 12 university hospitals. Yanagihara rating scale

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Sequence generation using envelope method.
Allocation concealment?	No	Not used - when entered in the trial, the allocation envelope contains the name of the treatment group
Blinding of participants?	No	Not done.
Blinding of assessors?	No	Not done.

Kawaguchi 2007 (*Continued*)

Incomplete outcome data?	Yes	Numbers of participants who did not complete clearly documented
Selective outcome reporting?	Yes	All primary outcomes reported.
Other sources of bias?	Yes	No other potential sources of bias identified.

Sullivan 2007

Methods	Double-blind, placebo-controlled randomized, factorial trial. Participants allocated to one of four treatment groups to receive either aciclovir, prednisolone, both agents or placebo
Participants	551 participants randomized and 496 included in final outcomes assessment. Referred for assessment and treatment within 72 hours of paralysis onset. All participants aged 16 or older and no contraindications to corticosteroids or antivirals
Interventions	Participants received prednisolone 25 mg twice daily for 10 days or aciclovir 400 mg five times daily for 10 days, both or neither depending upon allocation
Outcomes	Primary outcome measure was recovery rated on House-Brackmann scale where recovery was a score of H-B grade 1 Secondary outcomes included health-related quality of life, Health Utilities Index Mark 3, facial appearance (Derriford appearance scale) pain and adverse outcomes. Frequency of incomplete recovery at end of study was recorded Follow up at 3 and 9 months. Final outcomes reported at 9 months.
Notes	Multi-centre: 17 hospitals. House-Brackmann Scale.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote "...patient was randomly assigned to a study group by an independent, secure, automated telephone randomization service.."
Allocation concealment?	Yes	All parties blinded to allocation.
Blinding of participants?	Yes	Participants not receiving active drug given placebo. All administered medication identical and in identical containers
Blinding of assessors?	Yes	Assessors blinded to treatment group.
Incomplete outcome data?	Yes	All participants who were unable to complete are documented - both frequency and reason

Selective outcome reporting?	Yes	All planned outcome measures reported.
Other sources of bias?	Yes	No other potential sources of bias identified.

Yeo 2008

Methods	Randomized and double-blind. Two-arm design.
Participants	Included 91 participants with other causes of facial palsy excluded. No maximum period after onset stated but actual time to treatment recorded
Interventions	Randomized to receive either aciclovir and prednisolone or corticosteroids alone. aciclovir given at a dose of 2400 mg/day for 5 days. Prednisolone given as 1 mg/kg/day for 5 days then tapered on days 6 to 10. All participants admitted to hospital and received physical therapy and plasma volume expanders as adjuncts
Outcomes	Primary outcome was recovery on House-Brackmann (H-B) scale where recovery was taken as H-B <=2 Sub-group analysis of early versus delayed treatment. Follow up at 2 and 6 months. Final outcomes reported at 6 months.
Notes	Single centre. All participants admitted. Biased towards severe palsy. House-Brackmann Scale

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	States randomized in study title but no description of this in the article
Allocation concealment?	Unclear	No clear statement of this in the study.
Blinding of participants?	Unclear	States double-blind in study title but no description of methods employed for this in text
Blinding of assessors?	Unclear	States double-blind in study title but no description of methods employed for this in text
Incomplete outcome data?	Unclear	Incomplete follow-up data is not mentioned in the study.
Selective outcome reporting?	Yes	Stated primary outcome measure reported.
Other sources of bias?	No	Single centre study. All participants admitted. Biased towards cases of severe palsy.

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

Study	Reason for exclusion
Ahangar 2006	No random allocation to treatment groups.
Antunes 2000	Not enough information in original paper. Author contacted by Dr D Allen but no response received
Axelsson 2003	Use of a historical control group.
Chen 2005	Follow up data for four weeks from palsy onset only.
Hato 2003	Retrospective analysis of treatment.
Hultcrantz 2005	No random allocation to treatment groups.
Ibarrondo 1999	Retrospective study. One hundred participants collected between 1983 and 1989 received corticotherapy. One hundred participants treated after 1989 received aciclovir
P de Aquino 2001	Methodology not clear from original paper. Authors contacted by D Allen but no response. Confirmed by contacting D Allen in 2008 (PL)
Ramos Macias 1992	Inadequate allocation concealment. No information reported about methods of randomization; the diagnostic criteria used; the length of follow-up or number of participants lost to follow-up
Roy 2005	Inadequate information: abstract only published in journal supplement and not traced as a full publication
Zhou 1999	Prospective study. Sixty-nine participants with Bell's palsy followed up for 2 weeks only. Not double-blind and allocation concealment not described. Used own scale for palsy grading, outcome measures not met. Did report adverse events. Four aciclovir treatment participants had gastric malaise

Characteristics of studies awaiting assessment *[ordered by study ID]*

Inanli 2001

Methods	Prospective, controlled, randomized study
Participants	42 participants
Interventions	20 treated with aciclovir plus prednisone, 22 treated with prednisone alone
Outcomes	Neural regeneration
Notes	

DATA AND ANALYSES

Comparison 1. Antivirals versus placebo (including antivirals plus corticosteroids versus placebo plus corticosteroids or no treatment plus corticosteroids)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incomplete recovery at end of study	6	1886	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.65, 1.18]
1.1 Antivirals plus corticosteroids versus placebo plus corticosteroids or no treatment plus corticosteroids	6	1228	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.48, 1.05]
1.2 Antivirals versus placebo	2	658	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.80, 1.62]
2 Motor synkinesis or crocodile tears	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.20, 1.07]
3 Adverse Events	3	1544	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.38]

Comparison 2. Antivirals versus corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incomplete recovery at end of study	3	768	Risk Ratio (M-H, Random, 95% CI)	2.82 [1.09, 7.32]
2 Motor synkinesis at end of study	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.51, 2.07]
3 Adverse Events	2	667	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.65, 1.41]

Comparison 3. Antivirals plus corticosteroids versus placebo

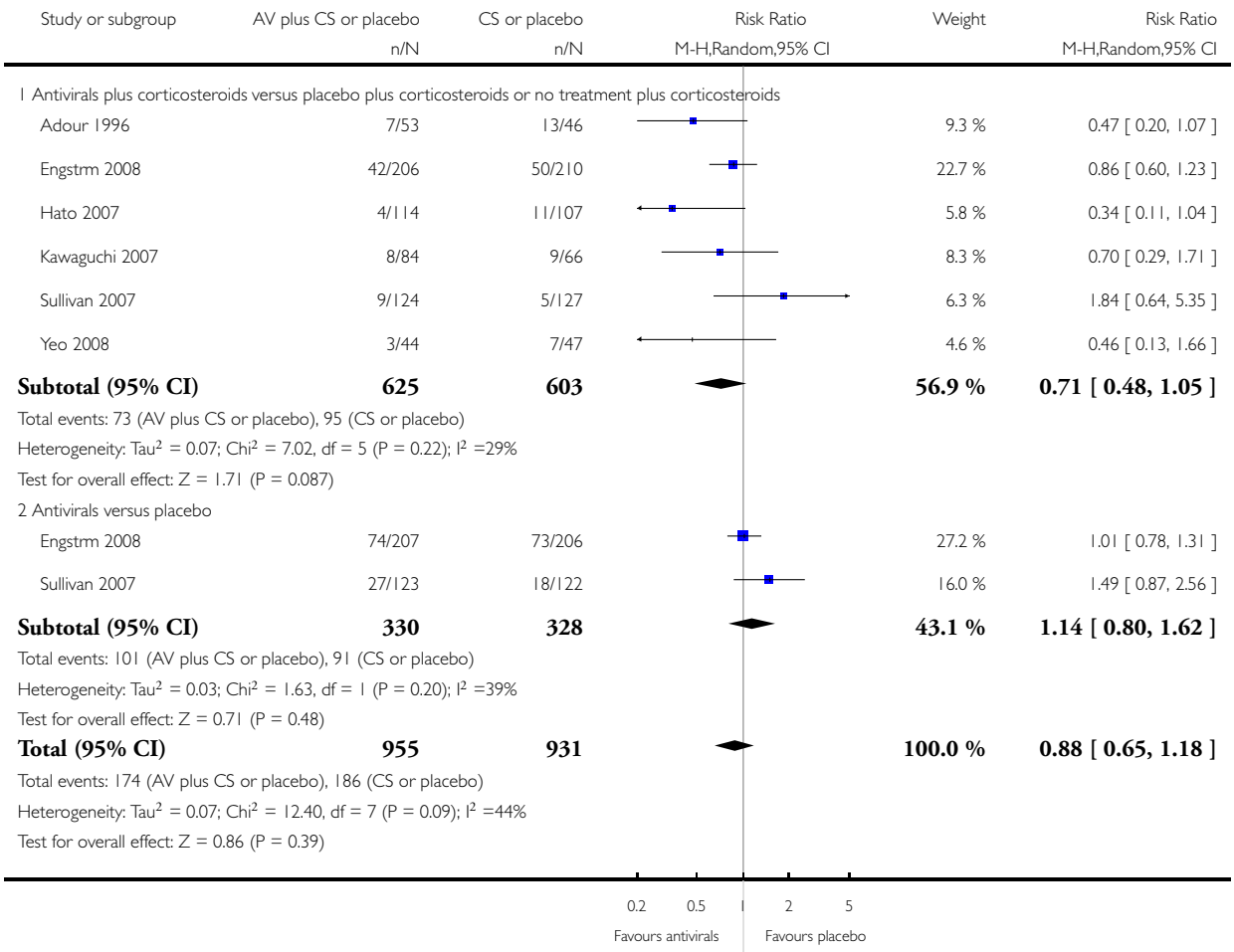
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incomplete recovery at end of study	2	658	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.41, 0.76]
2 Adverse Effects	2	658	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.79, 1.66]

Analysis 1.1. Comparison 1 Antivirals versus placebo (including antivirals plus corticosteroids versus placebo plus corticosteroids or no treatment plus corticosteroids), Outcome 1 Incomplete recovery at end of study.

Review: Antiviral treatment for Bell's palsy (idiopathic facial paralysis)

Comparison: 1 Antivirals versus placebo (including antivirals plus corticosteroids versus placebo plus corticosteroids or no treatment plus corticosteroids)

Outcome: 1 Incomplete recovery at end of study

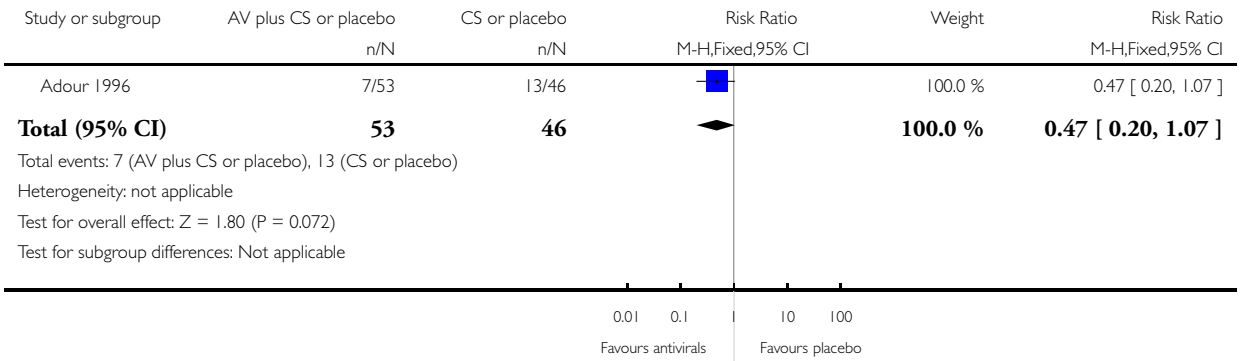


Analysis 1.2. Comparison 1 Antivirals versus placebo (including antivirals plus corticosteroids versus placebo plus corticosteroids or no treatment plus corticosteroids), Outcome 2 Motor synkinesis or crocodile tears.

Review: Antiviral treatment for Bell's palsy (idiopathic facial paralysis)

Comparison: 1 Antivirals versus placebo (including antivirals plus corticosteroids versus placebo plus corticosteroids or no treatment plus corticosteroids)

Outcome: 2 Motor synkinesis or crocodile tears

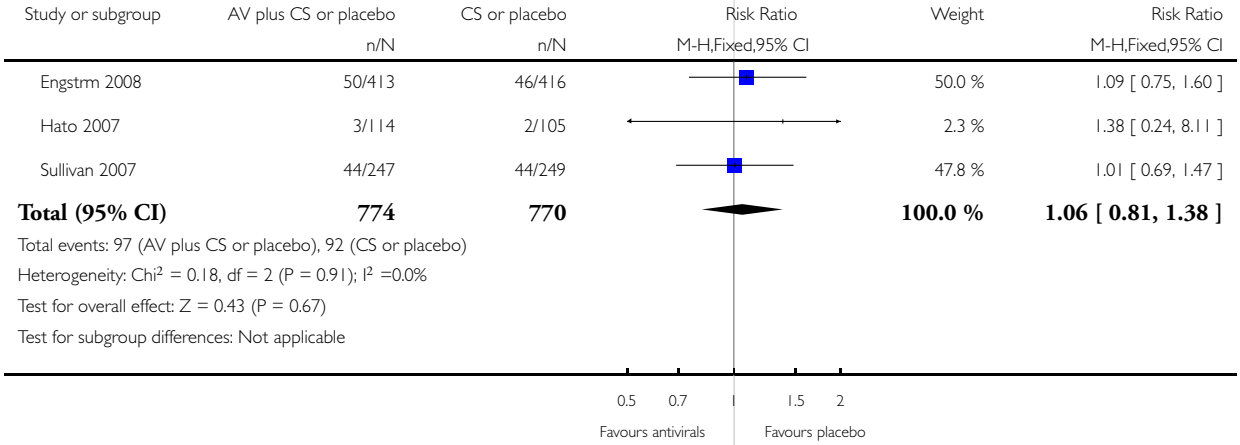


Analysis 1.3. Comparison 1 Antivirals versus placebo (including antivirals plus corticosteroids versus placebo plus corticosteroids or no treatment plus corticosteroids), Outcome 3 Adverse Events.

Review: Antiviral treatment for Bell's palsy (idiopathic facial paralysis)

Comparison: 1 Antivirals versus placebo (including antivirals plus corticosteroids versus placebo plus corticosteroids or no treatment plus corticosteroids)

Outcome: 3 Adverse Events

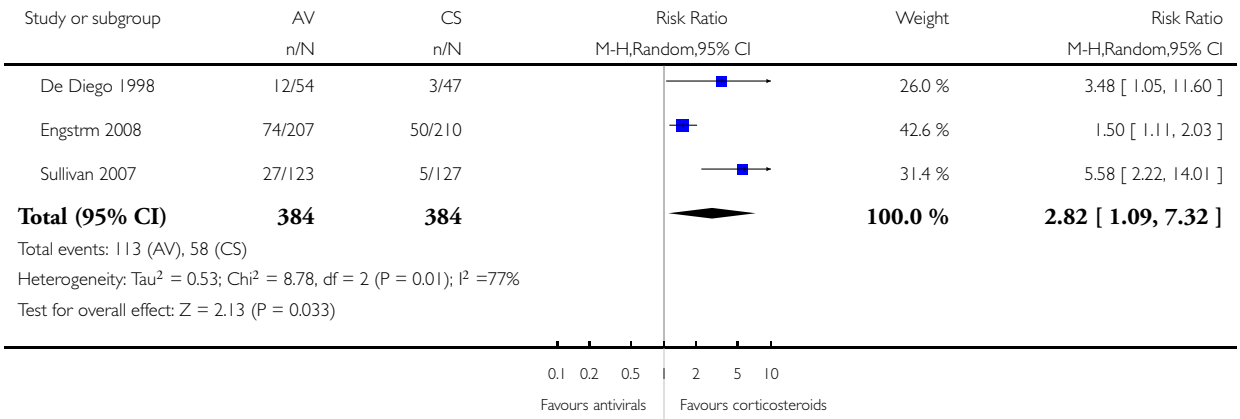


Analysis 2.1. Comparison 2 Antivirals versus corticosteroids, Outcome 1 Incomplete recovery at end of study.

Review: Antiviral treatment for Bell's palsy (idiopathic facial paralysis)

Comparison: 2 Antivirals versus corticosteroids

Outcome: 1 Incomplete recovery at end of study

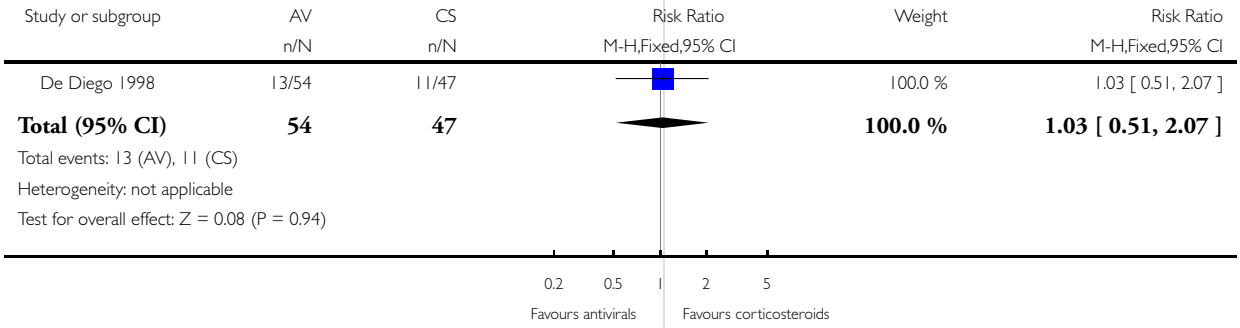


Analysis 2.2. Comparison 2 Antivirals versus corticosteroids, Outcome 2 Motor synkinesis at end of study.

Review: Antiviral treatment for Bell's palsy (idiopathic facial paralysis)

Comparison: 2 Antivirals versus corticosteroids

Outcome: 2 Motor synkinesis at end of study



Analysis 2.3. Comparison 2 Antivirals versus corticosteroids, Outcome 3 Adverse Events.

Review: Antiviral treatment for Bell's palsy (idiopathic facial paralysis)

Comparison: 2 Antivirals versus corticosteroids

Outcome: 3 Adverse Events

Study or subgroup	AV n/N	CS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Engstrm 2008	23/207	21/210		46.9 %	1.11 [0.63, 1.94]
Sullivan 2007	19/123	24/127		53.1 %	0.82 [0.47, 1.41]
Total (95% CI)	**330**	**337**		**100.0 %**	**0.96 [0.65, 1.41]**

Total events: 42 (AV), 45 (CS)

Heterogeneity: $Chi^2 = 0.59$, df = 1 (P = 0.44); $I^2 = 0.0\%$

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

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Antivirals plus corticosteroids versus placebo, Outcome 1 Incomplete recovery at end of study.

Review: Antiviral treatment for Bell's palsy (idiopathic facial paralysis)

Comparison: 3 Antivirals plus corticosteroids versus placebo

Outcome: 1 Incomplete recovery at end of study

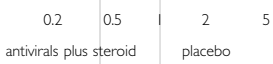
Study or subgroup	AV plus CS n/N	placebo/ no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Engstrm 2008	42/206	73/206		80.1 %	0.58 [0.41, 0.80]
Sullivan 2007	9/124	18/122		19.9 %	0.49 [0.23, 1.05]
Total (95% CI)	**330**	**328**		**100.0 %**	**0.56 [0.41, 0.76]**

Total events: 51 (AV plus CS), 91 (placebo/ no treatment)

Heterogeneity: $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 3.79 (P = 0.00015)

Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3 Antivirals plus corticosteroids versus placebo, Outcome 2 Adverse Effects.

Review: Antiviral treatment for Bell's palsy (idiopathic facial paralysis)

Comparison: 3 Antivirals plus corticosteroids versus placebo

Outcome: 2 Adverse Effects

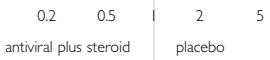
Study or subgroup	AV plus CS n/N	placebo/ no treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Engstrm 2008	27/206	25/206		55.4 %	1.08 [0.65, 1.80]
Sullivan 2007	25/124	20/122		44.6 %	1.23 [0.72, 2.09]
Total (95% CI)	**330**	**328**		**100.0 %**	**1.15 [0.79, 1.66]**

Total events: 52 (AV plus CS), 45 (placebo/ no treatment)

Heterogeneity: Chi^2 = 0.12, df = 1 (P = 0.73); I^2 =0.0%

Test for overall effect: Z = 0.73 (P = 0.46)

Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. House-Brackmann Scale

Grade	Description
I	Normal
II	Mild dysfunction; slight weakness noticeable only on close inspection; may have slight synkinesis
III	Moderate dysfunction; obvious but not disfiguring difference between the two sides; noticeable but not severe synkinesis
IV	Moderately severe dysfunction; obvious weakness and/or disfiguring asymmetry
V	Only barely perceptible motion
VI	No movement

House JW. Facial nerve grading systems. Laryngoscope 1983; 93: 1056-69.

House JW, Brackmann DE. Facial nerve grading system. Otolaryngology, Head and Neck Surgery 1985; 93: 146-7.

Table 2. Yanighara scale

Mode	Degree of paralysis				
	4 normal	**3** slight	**2** moderate	**1** severe	**0** total
At rest					
Wrinkle forehead					
Blink					
Normal closure of eye					
Forced closure of eye					
Closure of eye on involved side					
Wrinkle nose					
Whistle					
Grin					
Depress lower lip/ blow out cheek					

Ten separate categories of function, each scored 0 (total paralysis) to 4 (normal), then summed, giving a total score 0 (total paralysis) to 4 (normal), then summed, giving a total score from 0 (total paralysis) to 40 (normal function).

Yanighara N. Grading of facial palsy. Proc 3rd International Symposium on Facial Nerve Surgery, Zurich 1976. In Fish U., ed.Facial Nerve Surgery. Amstelveen, The Netherlands: Kugler Medical Publications 1977: 533-5.

Table 3. Sunnybrook Scale

Facial Grading System		
Resting Symmetry	**Symmetry of Voluntary Movement**	**Synkinesis**
Compared to Normal Side	Degree of muscle EXCURSION compared to normal side	Degree of INVOLUNTARY MUSCLE CONTRACTION associated with each expression
Eye	**STANDARD EXPRESSIONS** Forehead Wrinkle	**STANDARD EXPRESSIONS** Forehead Wrinkle

Table 3. Sunnybrook Scale (*Continued*)

		Gentle eye closure Open mouth smile Snarl Lip Pucker Score each out of 5, where 5 is normal and 1 is gross asymmetry/no movement)	Gentle eye closure Open mouth smile Snarl Lip Pucker Score each facial movement listed under standard expressions on a scale 0-3 where 0 is no asymmetry and 3 is severe asymmetry
	Normal = 0		
	Narrow = 1		
	Wide =1		
	Eyelid surgery = 1		
Cheek			
	Normal = 0		
	Absent = 2		
	Less pronounced = 1		
	More pronounced =1		
Mouth			
	Normal = 0		
	Corner drooped =1		
	Corner pulled up/out = 1		
TOTAL		TOTAL	TOTAL
Resting Symmetry Score x 5		**Voluntary Movement Score Total x 4**	**Synkinesis Score**
Voluntary Movement Score - Resting Symmetry Score - Synkinesis Score = Composite Score			

Weighted regional evaluation using five separate expressions. Composite score from 0 (total paralysis) to 100 (normal function). See Ross et al (1996).

Ross BG, Fradet G and Nedzelski JM. Development of a sensitive clinical facial grading system. Otolaryngol Head Neck Surg 1996; 114: 380-386.

APPENDICES

Appendix 1. MEDLINE search strategy

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized controlled trials/
4 random allocation/
5 double-blind method/
6 single-blind method/
7 or/1-6
8 animals/ not humans/
9 7 not 8
10 clinical trial.pt.
11 exp clinical trial/
12 (clin$ adj25 trial$).ti,ab.
13 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab.
14 placebos/
15 placebo$.ti,ab.
16 random$.ti,ab.
17 research design/
18 or/10-17
19 18 not 8
20 19 not 9
21 comparative study/
22 exp evaluation studies/
23 follow up studies/
24 prospective studies/
25 (control$ or prospectiv$ or volunteer$).ti,ab.
26 or/21-25
27 26 not 8
28 27 not (9 or 20)
29 9 or 20 or 28
30 exp Facial Nerve Diseases/
31 bell palsy/
32 facial paralysis/ or hemifacial spasm/
33 ((Bell$ or facial$ or hemifacial$ or unilateral$ or nerve$ or cranial$) adj3 (pals$ or paralys$ or paresi$ or spasm$)).mp. (21743)
34 30 or 31 or 32
35 34 or 33
36 Acyclovir/
37 exp Acyclovir/
38 (aciclovir$ or valaciclovir$).mp.
39 (acyclovir$ or valacyclovir$).mp.
40 36 or 37 or 38 or 39
41 29 and 35 and 40
42 limit 41 to ed=20071015-20081210
43 from 42 keep 1-5

Appendix 2. EMBASE search strategy

1 Randomized Controlled Trial/
2 Clinical Trial/
3 Multicenter Study/
4 Controlled Study/
5 Crossover Procedure/
6 Double Blind Procedure/
7 Single Blind Procedure/
8 exp RANDOMIZATION/
9 Major Clinical Study/
10 PLACEBO/
11 Meta Analysis/
12 phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/
13 (clin$ adj25 trial$).tw.
14 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.
15 placebo$.tw.
16 random$.tw.
17 control$.tw.
18 (meta?analys$ or systematic review$).tw.
19 (cross?over or factorial or sham? or dummy).tw.
20 ABAB design$.tw.
21 or/1-20
22 human/
23 nonhuman/
24 22 or 23
25 21 not 24
26 21 and 22
27 25 or 26
28 exp Nerve Paralysis/
29 bell palsy/
30 facial nerve paralysis/ or hemifacial spasm/
31 ((Bell$ or facial$ or hemifacial$ or unilateral$ or cranial$ or nerve$) adj3 (pals$ or paralys$ or paresi$ or spasm$)).mp.
32 or/28-31
33 ACICLOVIR/
34 (aciclovir$ or valaciclovir$).mp.
35 (acyclovir$ or valacyclovir$).mp.
36 33 or 34 or 35
37 27 and 32 and 36
38 limit 37 to em=200742-200850
39 from 38 keep 1-31

Appendix 3. LILACS search strategy

Facial Nerve Diseases or bell palsy or facial paralysis hemifacial spasm or ((Bell or bells or facial or hemifacial or unilateral or nerve or cranial) and (palsy or palsies or paralysis or paresi$ or spasm or spasms)) [Words] and Acyclovir or ganiclovir or aciclovir or valaciclovir or acyclovir or valacyclovir [Words] and ((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animals AND NOT (Ct humans and Ct animals)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animals AND NOT (Ct humans and Ct animals)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up

studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animals AND NOT (Ct humans and Ct animals))) [Words]

WHAT'S NEW

Last assessed as up-to-date: 24 February 2009.

Date	Event	Description
12 May 2010	Amended	Correction to reference

HISTORY

Protocol first published: Issue 3, 1999

Review first published: Issue 2, 2001

Date	Event	Description
10 November 2009	Amended	Correction of minor error in Discussion.
25 February 2009	New citation required and conclusions have changed	This is a substantive update to the previous edition of the review with a new review team. Five new studies added to the analysis with changes made to Results and Discussion sections as necessary
5 February 2009	New search has been performed	Substantive update to previous edition of review. Abstract and background information re-written. Modification of outcomes: all data from trials, whatever the trial length as opposed to 6 month outcomes. Five new studies added to the analysis with necessary changes made to Results and Discussion sections. One study removed from the previous review as no data contributed and none forthcoming to previous authors when approached
1 November 2007	Amended	Two trials, one with 551 participants comparing prednisolone with acyclovir with both and with neither, another with 221 participants comparing prednisolone and valacyclovir with prednisolone and placebo have just been published and will be included in an update of this review
1 March 2004	New citation required and conclusions have changed	Substantive amendment

(*Continued*)

1 January 2004	New search has been performed	The review was updated in January 2004. Searches were updated as follows: Neuromuscular Disease Group Trials Register (searched April 2003), MEDLINE (searched January 1966 to April 2003), EMBASE (searched January 1980 to April 2003), and LILACS (searched January 1982 to April 2003)

CONTRIBUTIONS OF AUTHORS

All authors contributed to the review and data extraction process. Dr F Daly wrote the first draft of the report with all clinical inputs from Professor F Sullivan and Dr P Lockhart. Dr P Lockhart incorporated the work into the existing review and was responsible for risk of bias assessment, data analysis and use of the RevMan software.

DECLARATIONS OF INTEREST

Dr F Daly and Professor F Sullivan are named authors on one of the included studies (Sullivan 2007).

SOURCES OF SUPPORT

Internal sources

- University of Dundee, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are several differences between the published review protocol and this version of the review. These mainly reflect the changes over time to the treatment options and Cochrane methodology. The search for studies now includes treatment with valaciclovir and famciclovir, either alone or in combination with any other therapy, to reflect the treatment options now available for Bell's palsy. The methodological assessment has been undertaken according to the latest Cochrane guidance, detailed in the Cochrane Handbook for Systematic Reviews of Interventions Chapter 8. Criteria for judging study quality are sequence generation, allocation concealment, blinding of participants and outcome assessors, selective outcome reporting and other sources of bias. The criteria are assessed as 'Yes', indicating a low likelihood of bias, 'No', indicating a high likelihood of bias or 'Unclear' where information is not sufficient to make a judgement. Other sources of bias which are considered includes diagnostic criteria, outcome criteria, baseline differences between groups and completeness of follow up. All five authors were given a selection of papers to read, review for quality and extract data from. The work was distributed so that each paper was reviewed by at least two authors. PL performed the final risk of bias quality assessment procedure which was independently reviewed by FS and FD.

We have focused this search on immunocompetent patients, which was not stipulated in the original protocol. This has been done as treatment protocols for immunocompromised individuals and treatment response may differ significantly from other individuals and, as such, cannot be fully explored in this analysis.

We have widened the outcome criteria to include outcomes at the end of the study as opposed to one year or six months after treatment. This is to allow inclusion of a maximal number of published studies. It is understood that this may introduce significant heterogeneity to the results and a sensitivity analysis looking at outcomes in participants in studies reporting at 12 weeks or less and six months or less was included in order to assess the influence this had on the robustness of published results.

INDEX TERMS

Medical Subject Headings (MeSH)

Acyclovir [analogs & derivatives; * therapeutic use]; Anti-Inflammatory Agents [therapeutic use]; Antiviral Agents [* therapeutic use]; Bell Palsy [*drug therapy; virology]; Drug Therapy, Combination [methods]; Herpes Simplex [complications; *drug therapy]; Prednisolone [therapeutic use]; Randomized Controlled Trials as Topic; Valine [analogs & derivatives; therapeutic use]

MeSH check words

Humans