Critical Review Form
Meta-analysis

Antiviral treatment for Bell's palsy (idiopathic facial paralysis)
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Objective: **"To determine the effectiveness of anti-herpes simplex antiviral treatments for Bell's palsy". (p. 3)**

Methods: **Five Cochrane authors independently searched the Cochrane Neuromuscular Disease Group Trials register, MEDLINE, EMBASE, and LILACS for trials of antiviral agents licensed to treat herpes simplex viral infections (acyclovir, valaciclovir or famciclovir) in immunecompetent patients with Bell's palsy. The primary outcome was incomplete recovering of facial function at the end of the study using one of several validated metrics (see below). Secondary outcomes include motor synkinesis or crocodile tears, complete facial paralysis, or adverse events at the end of the study.**

Bias potential was assessed using the 2008 Cochrane handbook quality assessment based upon method of randomization, amount/frequency/duration/administration route medication comparisons, blinding adequacy, and definition of recovery. When significant heterogeneity was detected ($I^2 > 50\%$), a random-effects model was used to generate summary relative risks. For adverse events the number of events (rather than number of patients affected) was used for analysis. Sensitivity analysis was conducted to assess the impact of combining steroids with antivirals and length of follow-up interval would have on the summary effect.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. Do anti-herpetic antiviral agents in Bell's palsy improve patient-important outcomes like incomplete long-term facial paralysis recovery?
2.	Was the search for relevant studies details and exhaustive?	Yes. Cochrane authors searched the Neuromuscular Disease Group Trials register, three electronic search engines, bibliographies, trial authors, and relevant drug companies.
3.	Were the primary studies of high methodological quality?	Fig 1, p. 6 Yes. Six of seven trials included (exception Yeo 2008) had low risk of significant bias.
4.	Were the assessments of the included studies reproducible?	Yes. "There were no disagreements about inclusion". (p. 4)

II.	***What are the results?***	
1.	What are the overall results of the study?	• Seven trials (Engström 2008, Hato 2007, Kawaguchi 2007, Sullivan 2007, Yeo 2008, Adour 1996, De Diego 1998) of 1987 participants were included using heterogeneous follow-up intervals and facial function outcome measures (House-Brackmann, Sunnybrook, Yanagihara). • Three trials evaluated in earlier Cochrane reviews on their topic were now excluded due to incomplete data (Antunes 2000, P de Aquino 2001, Roy 2005) after repeated attempts to elicit further details from the original investigators. • Study time-frames varied from three months (De Diego 1998), four months (Adour 1996), six months (Hato 2007, Kawaguchi 2007, Yeo 2008) nine months (Sullivan 2007), and 12 months (Engström 2008). • **Comparing antivirals versus placebo** – relative rate of incomplete recovery unaffected [RR 0.88 (95% CI 0.65-1.18)] with moderate heterogeneity (I^2 = 58%) so the random-effects model was used for meta-analysis. However, when analyzing the subset also treated with steroids (vs. steroids alone or placebo alone),there was a trend favoring the antiviral therapy fixed-effects RR0.64 (0.50-0.82), random-effects 0.71 (0.48-1.05) I^2 = 29%. • Antivirals and corticosteroids compared to corticosteroids alone had no effect on motor synkinesis or crocodile tears (RR 0.47, 95% CI 0.20 – 1.07). • No ↑ in adverse events (RR 1.06, 95% CI 0.81 – 1.38). Antivirals vs. Corticosteroids ○ Incomplete recovery was significantly less likely (worse outcome) in participants treated with antivirals than those treated with corticosteroids. (RR 2.82, 95% CI 1.09 – 7.32) with random-effects model and no effect on motor synkinesis/crocodile tears (RR 1.03, 95% CI 0.51 – 2.07) or adverse events (RR 0.96, 95% CI 0.65 – 1.41). Antivirals plus Corticosteriods vs. Placebo ○ Incomplete recovery favored combination therapy vs. placebo fixed effects RR 0.56 (95% CI 0.41 – 0.76) I^2 = 0% with no ↑ in adverse events noted RR 1.15 (95% CI 0.79 – 1.66) which the authors hypothesize could result from suppressed inflammatory mediator facial nerve tissue destruction by antiviral mediated Jarisch-Herxheimer reaction via steroid suppression. • Kawaguchi noted a lower recovery rate for those aged 40 – 60 compared with those under 40 years. • Sensitivity analysis assessing different responses to acyclovir or valacylovir did not alter treatment effects. • Removal of trial data with < 6 month follow-up data did not alter effect size either. • No data were available in any study to assess the outcome of complete paralysis at the end of the study.

2.	How precise are the results?	See CI above.
3.	Were the results similar from study to study?	No, many of the meta-analysis had significant heterogeneity ($I^2 > 50\%$) mandating random-effects analyses. The Cochrane authors hypothesize that "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". (p. 10) Also "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". (p. 14)
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	The majority of Bell's palsy patients do not benefit from antiviral therapy, either with or without corticosteroids. However, Hato and Kawaguchi both 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". (p. 14)
2.	Were all patient important outcomes considered?	No. "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". (p. 14)
3.	Are the benefits worth the costs and potential risks?	No. There is no significant evidence in the review to suggest a benefit let alone a cost-effective benefit for antiviral agents in treating Bells palsy. The Cochrane authors noted that a 10-day course of acyclovir costs £9.28 (US 2010 $14.50) and valaciclovir/ famciclovir significantly more. A 10-day course of prednisolone costs £7.14 pounds (US 2010 $11.15).

Limitations

1) **Insufficient available evidence for secondary outcomes or POEMS like QOL or perceived disability.**

2) **No stratified analysis via initial symptom severity or duration of illness prior to treatment.**

3) **No assessment of publication bias.**

4) **No assessment of the gray literature (see PGY-III paper).**

5) **Over half of the subjects come from two studies, although the overall results were robust to sensitivity analysis.**

Bottom Line

Available research data, including seven high quality trials of 1987 patients, do not suggest a benefit for anti-herpetic agents (acyclovir, valacylovir, famciclovir) in the acute management of Bell's palsy. The one exception (supported by two trials) may be the subset with complete unilateral facial paralysis on presentation in which case recovery rates may improve with antivirals and steroids vs. steroids alone. Future trials will need to assess the role of antivirals this subset in addition to patient-oriented outcomes like QOL and perceived disability.