Critical Review Form
Meta-analysis

Combined Corticosteroid and Antiviral Treatment for Bell Palsy
A Systematic Review and Meta-analysis *JAMA* 2009; 302:985-933

Objective: **To evaluate the "evidence of the association of corticosteroid and antiviral agent therapy with the risks of unsatisfactory facial recovery, synkinesis and autonomic dysfunction, and adverse effects in patients with Bell palsy". (p. 986)**

Methods: **Searched a variety of electronic databases (MEDLINE, EMBASE, CENTRAL, CINAHL, PsychInfo and Web of Science) for peer-reviewed research publications as well as non-peer reviewed reports like conference proceedings or dissertations (PAPERSFIRST, PROCEEDINGS FIRST, PROQUEST). The SR authors also screened bibliographics, contacted experts, and checked the clinical trial registry (www.clinicaltrials.gov). Two reviewers independently screened all studies retrieved for inclusion criteria: RCT of Bell's palsy patients treated with corticosteroid or antiviral agents against a control that reported at least one outcome of facial recovery, synkinesis, autonomic dysfunction or adverse effects. Non-English studies were translated and when data were incomplete original investigators were contacted.**

Methodological biases (adequacy of random sequence generation, allocation concealment, blinding, loss to follow-up and selective reporting) were evaluated according to the Cochrane criteria guidelines. Additionally, the SR authors considered issues of risk of bias, precision, consistency, directness, and publication bias as per the GRADE working group. The primary outcome was unsatisfactory facial recovery at or beyond four months post-treatment.

The SR authors hypothesized five explanations for variability *a priori*.

1) **Treatment modality (larger effect in trials combining antiviral and corticosteroids than either alone).**
2) **Dose – smaller benefit with < 450 mg prednisolone equivalent or < 4000 mg/d acyclovir or < 3000 mg/d valacylovir.**

3) **Time to treatment – larger benefit when treated within 72-hours of symptom onset.**
4) **Initial severity – greater benefit in moderate vs. severe.**
5) **Blinding.**

Pooled effect size was derived using a random effect model. Publication bias was assessed using funnel plots and the Egger statistic. To explore the interaction between corticosteroids and antiviral agents, the authors used logistic regression analysis with study, corticosteroid treatment, antiviral agent treatment, and an interaction term for corticosteroid and antiviral treatment as co-variates.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. What is the evidence for steroids, antiviral agents, both or neither in alleviating the unwanted sequelae of Bell's palsy?
2.	Was the search for relevant studies details and exhaustive?	Absolutely. Even more thorough then the Cochrane search strategies. However, the authors do not describe the encompassing years of their electronic search strategies and missed the Taverner 1954 RCT captured in the Cochrane review. They might have noted this miss had they included the Cochrane registry among their search strategies. As it is, they identified and included 10 additional RCT's then the Cochrane review on antivirals (Adour, Hato, Inanli, Kawaguchi, Roy, Vazquez, Wolf, Yeo, Antunes, and Tekle-Haimanot) although some of these were deliberately excluded from the Cochrane reviews because they did not compare steroids or antivirals to biologically inert placebos.
3.	Were the primary studies of high methodological quality?	Yes. "The quality of evidence was high for the effects of corticosteroids on unsatisfactory facial recovery and on synkinesis and autonomic dysfunction. The quality of the evidence was moderate for other outcomes". (p. 989)
4.	Were the assessments of the included studies reproducible?	Yes. "Interrater agreement for study inclusion was excellent ($\kappa = 0.88$)". (p. 988) "Interrater agreement for assessment of methodological quality ranged from 0.58 to 1.00 for the categories… (p. 988 – see Table 2).

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<tr><th>II.</th><th>What are the results?</th><th></th></tr>
<tr><td>1.</td><td>What are the overall results of the study?</td><td>

18 trials including 2786 patients were included with median six months follow-up from 12 counties on five continents. All but seven trials were patients older than 14 years of age.
Original authors were successfully contacted in 9/16 cases where information was needed and trial results were verified in 4/5 cases.
In four trials the loss to follow-up exceeded 20%.

Effect sizes (Table 3, p. 989) or unsatisfactory facial recovery:
<table>
<tr><th></th><th>RR</th><th>NNT
95% CI</th><th>Quality of
Evidence</th></tr>
<tr><td>Corticosteroids alone</td><td>0.69
(0.55-.0.87)</td><td>11
(8-25)</td><td>High</td></tr>
<tr><td>Antiviral agents alone</td><td>1.14
(0.80-1.62)</td><td>25
(17- ∞)</td><td>Moderate</td></tr>
<tr><td>Corticosteroids + Antiviral agents*</td><td>0.48
(0.29-0.79)</td><td>6
(4-14)</td><td>Moderate</td></tr>
</table>
*vs. antiviral agents alone.
<hr>

<u>Corticosteroids also reduced the incidence of synkinesis and autonomic dysfunction</u> (NNT 7, 95% CI 6 – 10 – High quality evidence), but antiviral agents had no effect on these secondary outcomes.
A significant interaction was noted between higher doses and lower doses of steroids – deemed by the authors as credible but not definitive because “the effect is not likely to be due to chance, is relatively large, has biological plausibility, and is consistent across studies”. (p. 991)
<u>Adverse effects were not associated with corticosteroids or antiviral agents including no cases of a vascular necrosis</u>.
No evidence of publication bias was detected.

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<tr><td>2.</td><td>How precise are the results?</td><td>Yes. See CI reported above.</td></tr>
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3.	Were the results similar from study to study?	Yes. See Fig 2 (p. 990) demonstrating that for corticosteroids 9/11 trials' point estimates favor steroid therapy. Similarly 2/2 antiviral trials show no benefit.
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?	"Bell palsy may best be managed with corticosteroids and that antiviral agents may be of no benefit". (p. 990)
2.	Were all patient important outcomes considered?	No studies assessed patient-oriented evidence like QDL or perceived disability.
3.	Are the benefits worth the costs and potential risks?	"The cost of roughly $20 per day for acyclovir (4000 mg) and valacyclovir (3000 mg) is not insignificant. The higher value that patients place on the uncertain incremental benefit of combining antiviral agents and corticosteroids compared with corticosteroids alone is likely to determine their inclination to use antiviral agents in addition to corticosteroids". (p. 992)

Limitations

1) **Two trials contributed almost half of the patients however, results were consistent across studies and the SR authors used the more conservation random-effects modeling. Nonetheless, the SR authors could have conducted a sensitivity analysis to test the robustness of their conclusions.**

2) **Subjective primary outcome measured by a variety of "validated" instruments, although one recent review suggested that three of the scales show moderate agreement (ref 50).**

3) **Insufficient evidence to evaluate POEMS like Quality of Life or time to recovery.**

4) **No assessment of subgroups (pediatric, geriatric, onset > 72°) with variable prognosis for full-recovery from Bell's Palsy.**

Bottom Line

High quality evidence does not support the use of antiviral agents alone, but corticosteroids alone reduce poor cosmetic outcome rates (NNT = 11) and synkinesis crocodile tears (NNT 7). The addition of antiviral agents to steroids may provide an incremental benefit in reducing poor cosmetic outcomes, but the evidence is not conclusive. Steroids should be used in doses exceeding 450 mg equivalent of prednisolone.