

# Combined Corticosteroid and Antiviral Treatment for Bell Palsy

## A Systematic Review and Meta-analysis

John R. de Almeida, MD

Murtadha Al Khabori, MD

Gordon H. Guyatt, MD, MSc, FRCPC

Ian J. Witterick, MD, MSc, FRCSC

Vincent Y. W. Lin, MD, FRCSC

Julian M. Nedzelski, MD, FRCSC

Joseph M. Chen, MD, FRCSC

**B**ELL PALSY OR IDIOPATHIC FACIAL paralysis, an acute weakness or paralysis of the facial nerve, has a lifetime risk of 1 in 60.<sup>1</sup> The annual incidence of Bell palsy is 20 to 30 per 100 000 population.<sup>2</sup> While 71% of untreated patients will completely recover and 84% will have complete or near normal recovery,<sup>3</sup> the remainder will have persistent moderate to severe weakness, facial contracture, or synkinesis.<sup>1</sup> Initial severity is associated with a poor prognosis with as few as 61% of cases of complete pareses and as many as 94% of cases of incomplete pareses having complete recovery,<sup>3</sup> usually within 4 months of presentation.<sup>3,4</sup>

A herpes infection likely causes this disorder.<sup>5-9</sup> Swelling of the nerve at the meatal foramen has been observed intraoperatively,<sup>10</sup> and sampling of endoneurial fluid during nerve decompression for Bell palsy has yielded DNA of herpes sim-

**Context** New evidence has emerged regarding the use of corticosteroids and antiviral agents in Bell palsy.

**Objective** To estimate the association of corticosteroids and antiviral agents with the risk of unsatisfactory facial recovery in patients with Bell palsy.

**Data Sources** The search included MEDLINE, EMBASE, CENTRAL, PsychInfo, CINAHL, Web of Science, PAPERSFIRST, PROCEEDINGSFIRST, and PROQUEST to identify studies up to March 1, 2009.

**Study Selection and Data Extraction** Eligible studies were randomized controlled trials comparing treatment with either corticosteroids or antiviral agents with a control and measuring at least 1 of the following outcomes: unsatisfactory facial recovery ( $\geq 4$  months), unsatisfactory short-term recovery (6 weeks to  $< 4$  months), synkinesis and autonomic dysfunction, or adverse effects. Two reviewers extracted data on study characteristics, methods, and outcomes. Disagreement was resolved by consensus.

**Results** Eighteen trials involving 2786 patients were eligible. Regression analysis identified a synergistic effect when corticosteroids and antiviral agents were administered in combination compared with alone (odds ratio for interaction term, 0.54 [95% confidence interval {CI}, 0.35-0.83];  $P = .004$ ). Meta-analysis using a random-effects model showed corticosteroids alone were associated with a reduced risk of unsatisfactory recovery (relative risk [RR], 0.69 [95% CI, 0.55-0.87];  $P = .001$ ) (number needed to treat to benefit 1 person, 11 [95% CI, 8-25]), a reduced risk of synkinesis and autonomic dysfunction (RR, 0.48 [95% CI, 0.36-0.65];  $P < .001$ ) (number needed to treat to benefit 1 person, 7 [95% CI, 6-10]), and no increase in adverse effects. Antiviral agents alone were not associated with a reduced risk of unsatisfactory recovery (RR, 1.14 [95% CI, 0.80-1.62];  $P = .48$ ). When combined with antiviral agents, corticosteroids were associated with greater benefit (RR, 0.48 [95% CI, 0.29-0.79];  $P = .004$ ) than antiviral agents alone. When combined with corticosteroids, antiviral agents were associated with greater risk reduction of borderline significance compared with corticosteroids alone (RR, 0.75 [95% CI, 0.56-1.00];  $P = .05$ ).

**Conclusions** In Bell palsy, corticosteroids are associated with a reduced risk of unsatisfactory recovery. Antiviral agents, when administered with corticosteroids, may be associated with additional benefit.

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**Author Affiliations:** Department of Otolaryngology-Head and Neck Surgery, Sunnybrook Hospital (Drs de Almeida, Lin, Nedzelski, and Chen), Department of Medical Oncology and Hematology, Princess Margaret Hospital (Dr Al Khabori), and Department of Otolaryngology-Head and Neck Surgery, Mount Sinai Hospital (Dr Witterick), University of Toronto, Toronto, Ontario, Canada; and Departments of Clinical Epidemiology and Biostatistics (Drs de Almeida, Al Khabori, and Guyatt) and Medicine (Dr Guyatt), CLARITY Research Group

(Dr Guyatt), McMaster University, Hamilton, Ontario, Canada.

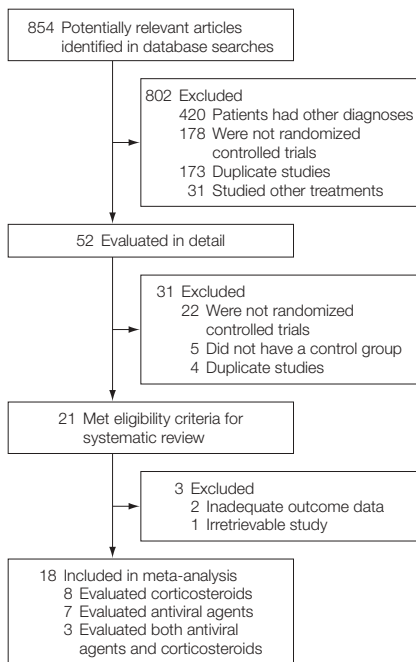
**Corresponding Author:** Gordon H. Guyatt, MD, MSc, FRCPC, McMaster University, Health Sciences Center, 2C12, 1200 Main St W, Hamilton, ON, Canada L8N 3Z5 (guyatt@mcmaster.ca).

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and questions on p 1010.

**Figure 1.** Selection of Studies for Meta-analysis

The search was conducted with the MEDLINE, EMBASE, CENTRAL, CINAHL, PsychInfo, Web of Science, PAPERSFIRST, PROCEEDINGSFIRST, and PROQUEST databases to identify studies up to March 1, 2009.

plex virus type 1 (HSV-1).<sup>9</sup> Varicella zoster virus (VZV) reactivation is also associated with Bell palsy<sup>11,12</sup> and may be responsible for as many as one-third of idiopathic facial paralyses.<sup>13</sup>

The goal of treatment for Bell palsy is preventing sequelae. Both corticosteroids and antiviral agents are used as treatment strategies. In a large observational study from the United Kingdom, 36% of patients with Bell palsy were prescribed corticosteroids, 0.6% were prescribed antiviral agents, and 0.4% were prescribed a combination, suggesting the clinical community is unconvinced of the benefit of these agents.<sup>14</sup> However, recent Cochrane systematic reviews have failed to show benefit for either treatment.<sup>15,16</sup> Prior systematic reviews demonstrated a modest effect of corticosteroids,<sup>17,18</sup> but either included non-randomized controlled trials (non-RCTs)<sup>17</sup> or excluded trials meeting their own eligibility criteria.<sup>18</sup> Several RCTs recently have been completed,<sup>19-25</sup> includ-

ing 2 large trials (N=839 and N=551)<sup>19,23</sup> that both demonstrated benefit with corticosteroids but not with antiviral agents.

We conducted a systematic review and meta-analysis, including the most recent 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.

## METHODS

We searched MEDLINE, EMBASE, CENTRAL, CINAHL, PsychInfo, and Web of Science to March 1, 2009, for relevant trials in any language. Our search included the gray literature (conference proceedings, dissertations, and theses) through PAPERSFIRST, PROCEEDINGSFIRST, and PROQUEST. We screened bibliographies of relevant articles, involved experts (V.Y.W.L., J.M.N., J.M.C.), and checked the clinical trial registry ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) for additional studies. Medical Subject Headings and keywords for methods (RCTs), patient population (Bell palsy and idiopathic facial nerve paralysis occurring at all ages), and interventions (corticosteroids and antiviral agents) were used to identify studies.

Two reviewers (J.R.D., M.A.) independently screened all studies by title or abstract for those requiring further retrieval (full text or abstract), and then independently reviewed these studies for eligibility (FIGURE 1). The inclusion criterion was a RCT study design of patients diagnosed with Bell palsy. Included studies compared treatment with corticosteroids or antiviral agents against a control (placebo, no treatment, supportive treatment, an active treatment present in both groups) and reported at least 1 of the outcomes of facial recovery, synkinesis and autonomic dysfunction, major adverse effects, and/or minor adverse effects. Disagreements regarding trial eligibility were resolved by consensus.

Studies in non-English languages were translated. Two reviewers (J.R.D., M.A.)

extracted data and resolved inconsistencies by consensus. We attempted to contact primary authors for further information regarding study inclusion, methods, outcomes, and verification of trial results. We recorded patient eligibility, number of patients, and treatment in each group. We addressed methodological quality including adequacy of random sequence generation, allocation concealment, blinding, loss to follow-up, selective reporting, or other biases. Judgments regarding the presence of methodological biases were made according to the Cochrane criteria guidelines.<sup>26</sup> As suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group, we considered issues of risk of bias, precision, consistency, directness, and publication bias in determining the quality of evidence for each outcome.<sup>27</sup>

The primary outcome measure was unsatisfactory facial recovery ( $\geq 4$  months); secondary outcomes included unsatisfactory short-term recovery (6 weeks to  $< 4$  months), synkinesis and autonomic dysfunction, major life-threatening adverse effects, and minor adverse effects. When outcomes were reported at multiple time points, we used the earliest time point for the short-term outcome and the latest time point for the primary outcome.

To explain variability in the primary outcome, we defined 5 a priori hypotheses: treatment modality (larger effect in combination vs corticosteroid or antiviral agent monotherapy), initial severity (greater benefit in moderate vs severe paresis), dose (smaller benefit in cumulative dose of  $< 450$  mg vs  $\geq 450$  mg of prednisone equivalent for corticosteroids and smaller benefit for  $< 4000$  mg/d of acyclovir or  $< 3000$  mg/d of valacyclovir vs  $\geq 4000$  mg/d of acyclovir or  $\geq 3000$  mg/d valacyclovir), time to treatment (larger benefit in studies in which patients were treated within 72 hours vs studies in which patients were not necessarily treated within 72 hours), and blinding.

Studies used a variety of measurement instruments including the House-Brackmann, Facial Paralysis Recovery

Profile/Index, Sunnybrook, Yanagihara, Modified Adour Mechelse, and instruments<sup>28-32</sup> not previously described to measure recovery and initial severity (eTable [available at <http://www.jama.com>] and TABLE 1). We defined unsatisfactory recovery as failure to achieve complete or near normal recovery. In 2 studies, investigators reported outcomes using 2 instruments, one of which was the House-Brackmann. For these studies, we report the House-Brackmann results.

We measured interrater agreement for study inclusion and assessment of methodological quality (weighted  $\kappa$ ). We report outcomes using relative risks (RR) with 95% confidence intervals (CIs). Pooled estimates of effect were derived using a random-effects model with Mantel-Haenszel statistics. Study heterogeneity was determined using the  $I^2$  statistic in which 0% to 40% may be unimportant heterogeneity, 30% to 60% indicates moderate, 50% to 90% indicates substantial, and 75% to 100% indicates considerable heterogeneity<sup>44</sup> and the  $P$  value from the  $\chi^2$  test. Trials with factorial design were treated as 2 separate trials (combined therapy vs monotherapy, placebo and monotherapy, or placebo vs double placebo).

To explore the interaction between corticosteroids and antiviral agents, we used logistic regression analysis with study, corticosteroid treatment, antiviral agent treatment, and an interaction term for corticosteroid and antiviral agent treatment as covariates. For other a priori hypotheses, we calculated  $z$  scores to test for interactions.<sup>45</sup> We estimated event rates (baseline risk for unsatisfactory recovery) in untreated patients from previous observational data,<sup>3</sup> and from the median control group event rate for all other outcomes. Corresponding risks with 95% CIs were computed by multiplying treatment effect (RR) and control event rates. The absolute risk reduction was calculated as the difference of baseline and corresponding risk. The number of patients needed to treat for 1 patient to experience benefit (NNTB) or harm (NNTH) were computed by

taking the reciprocal of the absolute risk reduction or absolute risk increase.<sup>46</sup>

Publication bias was evaluated using funnel plots and the Egger statistic for unsatisfactory recovery. Regression analysis was performed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois), meta-analyses were performed using Review Manager version 5.0.17 (Nordic Cochrane Center, Copenha-

gen, Denmark), and Egger statistical analyses were performed using Stata version 10.0 (StataCorp, College Station, Texas).

## RESULTS

Of 854 identified studies, 18 were eligible for inclusion (Figure 1). Of these, 8 evaluated corticosteroids, 7 evaluated antiviral agents, and 3

**Table 1.** Study Characteristics of Randomized Controlled Trials Included in the Meta-analysis

| Source                              | Randomization Groups                | No. of Patients Randomized |
|-------------------------------------|-------------------------------------|----------------------------|
| Adour et al, <sup>33</sup> 1996     | Placebo plus prednisone             | 46                         |
|                                     | Acyclovir plus prednisone           | 53                         |
| Antunes et al, <sup>34</sup> 2000   | Double placebo                      | 17                         |
|                                     | Placebo plus deflazacort            | 14                         |
|                                     | Valacyclovir plus deflazacort       | 15                         |
| Austin et al, <sup>35</sup> 1993    | Placebo                             | 41                         |
|                                     | Prednisone                          | 35                         |
| Bento et al, <sup>36</sup> 1991     | Placebo                             | 20                         |
|                                     | Dexamethasone                       | 20                         |
| Engström et al, <sup>19</sup> 2008  | Double placebo                      | 209                        |
|                                     | Placebo plus prednisolone           | 213                        |
|                                     | Valacyclovir plus placebo           | 207                        |
|                                     | Valacyclovir plus prednisolone      | 210                        |
| Hato et al, <sup>20</sup> 2007      | Placebo plus prednisone             | 107                        |
|                                     | Valacyclovir plus prednisone        | 114                        |
| Inanli et al, <sup>37</sup> 2001    | Prednisone alone                    | 22                         |
|                                     | Acyclovir plus prednisone           | 20                         |
| Kawaguchi et al, <sup>21</sup> 2007 | Placebo plus prednisolone           | 66                         |
|                                     | Valacyclovir plus prednisolone      | 84                         |
| Lagalla et al, <sup>38</sup> 2002   | Placebo plus polyvitamin therapy    | 28                         |
|                                     | Prednisone plus polyvitamin therapy | 30                         |
| Martinez et al, <sup>39</sup> 1990  | No placebo                          | 45                         |
|                                     | Prednisone                          | 42                         |
| May et al, <sup>40</sup> 1976       | Vitamins                            | 26                         |
|                                     | Vitamins plus prednisone            | 25                         |
| Roy et al, <sup>22</sup> 2005       | Methylprednisolone alone            | 32                         |
|                                     | Acyclovir plus methylprednisolone   | 32                         |
| Sullivan et al, <sup>23</sup> 2007  | Double placebo                      | 141                        |
|                                     | Placebo plus prednisolone           | 138                        |
|                                     | Acyclovir plus placebo              | 138                        |
|                                     | Acyclovir plus prednisolone         | 134                        |
| Tekle-Haimanot, <sup>41</sup> 1987  | Vitamins                            | 29                         |
|                                     | Prednisone                          | 30                         |
| Unüvar et al, <sup>42</sup> 1999    | No placebo                          | 21                         |
|                                     | Methylprednisolone                  | 21                         |
| Vazquez et al, <sup>24</sup> 2008   | Placebo plus prednisone             | 19                         |
|                                     | Valacyclovir plus prednisone        | 22                         |
| Wolf et al, <sup>43</sup> 1978      | No placebo                          | 132                        |
|                                     | Prednisone                          | 107                        |
| Yeo et al, <sup>25</sup> 2008       | Prednisone alone                    | 47                         |
|                                     | Acyclovir plus prednisone           | 44                         |

evaluated both corticosteroids and antiviral agents. Interrater agreement for study inclusion was excellent ( $\kappa=0.88$ ).

The 18 trials included 2786 patients (mean, 155 patients; range, 40-829), 2078 in corticosteroid trials, and 2134 in antiviral agent trials. Median follow-up was 6 months (range, 10 weeks-12 months). Trials were conducted in 12 countries and 5 continents. Thirteen studies were published in English, 2 in Portuguese,<sup>34,36</sup> 2 in Spanish,<sup>24,39</sup> and 1 in Turkish.<sup>37</sup> All but 3 trials<sup>33,34,39</sup> attempted to rule out other causes of acute facial paralysis. One trial involved exclusively pediatric patients,<sup>42</sup> 6 trials included pediatric patients,<sup>22,34,36,39,42,43</sup> and the remainder included only patients older than 14 years.

Eight trials compared corticosteroids with a control (placebo, supportive treatment, or no treatment),<sup>35,36,38-43</sup>

7 compared the combination of antiviral agents and corticosteroids with a corticosteroid control (with or without placebo),<sup>20-22,24,25,33,37</sup> 2 used a factorial design,<sup>19,23</sup> and 1 used a 3-group design comparing the combination of antiviral agents and corticosteroids vs corticosteroids and placebo vs double placebo (eTable [available at <http://www.jama.com>] and Table 1).<sup>34</sup>

We attempted to contact 16 primary authors,<sup>19-25,33-39,41,42</sup> and established contact with 9.<sup>20-24,33,35,36,38</sup> Information regarding study inclusion was sought and retrieved from 3 trials.<sup>21,22,24</sup> Methodological information was sought from 13 trials<sup>20-22,25,33-39,41,42</sup> and retrieved from 7.<sup>20-22,33,35,36,38</sup> Further outcome results were requested from investigators for 15 trials<sup>19-23,25,33-39,41,42</sup> and obtained from 4.<sup>20-22,38</sup> Attempts to verify trial results was successful in 4<sup>20,22,23,33</sup> of 5 trials.<sup>20,22,23,33,34</sup> Unpublished results were obtained for the primary outcome in 1 trial,<sup>21</sup> unsatisfac-

tory recovery (short term) in 3 trials,<sup>20-22</sup> and major adverse effects in 1 trial.<sup>22</sup>

TABLE 2 reports risk of bias<sup>26</sup> for each trial. Interrater agreement for assessment of methodological quality ranged from 0.58 to 1.00 for the 6 categories with an overall agreement of 0.75. The lowest agreement was in the category of other bias, while perfect agreement was achieved in the areas of adequate sequence generation and allocation concealment. Although all studies describe randomization, 6 did not adequately describe methods of random sequence generation,<sup>25,34,37,39,41,43</sup> and 7 did not adequately describe allocation concealment.<sup>25,34,37,39,41-43</sup> Ten studies used blinding methods for outcome adjudication.<sup>19,23-25,33-36,38,40</sup> Five trials described the type of analysis<sup>19-21,23,38</sup>, one described adherence to the intention-to-treat principle.<sup>23</sup> Five trials described a modified intention-to-treat analysis.<sup>19-21,24,38</sup> One trial described a

**Table 2.** Assessment of Study Quality

| Source                              | Adequate Sequence Generation | Allocation Concealment | Blinding | Incomplete Outcome Data Addressed | Free of Selective Reporting | Free of Other Bias | Description of Other Bias   |
|-------------------------------------|------------------------------|------------------------|----------|-----------------------------------|-----------------------------|--------------------|---|
| Adour et al, <sup>33</sup> 1996     | Yes                          | Yes                    | Yes      | Unclear                           | No                          | No                 | Use of per-treatment analysis   |
| Antunes et al, <sup>34</sup> 2000   | Unclear                      | Unclear                | Yes      | Yes                               | No                          | No                 | Poorly described statistical methods  |
| Austin et al, <sup>35</sup> 1993    | Yes                          | Yes                    | Yes      | No                                | No                          | No                 | Prognostically imbalanced groups; more severe pareses in control group              |
| Bento et al, <sup>36</sup> 1991     | Yes                          | Yes                    | Yes      | No                                | Yes                         | No                 | Poorly described statistical methods  |
| Engström et al, <sup>19</sup> 2008  | Yes                          | Yes                    | Yes      | No                                | Yes                         | No                 | Premature trial termination; modified intention-to-treat analysis; industry funding |
| Hato et al, <sup>20</sup> 2007      | Yes                          | Yes                    | No       | No                                | Yes                         | No                 | Postrandomization exclusion of patients with varicella zoster virus                 |
| Inanli et al, <sup>37</sup> 2001    | Unclear                      | Unclear                | No       | Yes                               | Yes                         | Yes                |   |
| Kawaguchi et al, <sup>21</sup> 2007 | Yes                          | Yes                    | No       | Yes                               | Yes                         | No                 | Postrandomization exclusion of patients with varicella zoster virus                 |
| Lagalla et al, <sup>38</sup> 2002   | Yes                          | Yes                    | Yes      | Yes                               | No                          | No                 | Postrandomization exclusion of patients with varicella zoster virus                 |
| Martinez et al, <sup>39</sup> 1990  | Unclear                      | Unclear                | No       | No                                | Yes                         | Yes                |   |
| May et al, <sup>40</sup> 1976       | Yes                          | Yes                    | Yes      | Yes                               | No                          | Yes                |   |
| Roy et al, <sup>22</sup> 2005       | Yes                          | Yes                    | No       | Yes                               | Yes                         | Yes                |   |
| Sullivan et al, <sup>23</sup> 2007  | Yes                          | Yes                    | Yes      | Yes                               | Yes                         | Yes                |   |
| Tekle-Haimanot, <sup>41</sup> 1987  | Unclear                      | Unclear                | No       | Yes                               | Yes                         | No                 | Poorly described statistical methods  |
| Unüvar et al, <sup>42</sup> 1999    | Yes                          | Unclear                | No       | Yes                               | Yes                         | Yes                |   |
| Vazquez et al, <sup>24</sup> 2008   | Yes                          | Yes                    | Yes      | Yes                               | No                          | No                 | Modified intention-to-treat analysis  |
| Wolf et al, <sup>43</sup> 1978      | Unclear                      | Unclear                | No       | Unclear                           | Yes                         | Yes                |   |
| Yeo et al, <sup>25</sup> 2008       | Unclear                      | Unclear                | Yes      | Yes                               | Yes                         | Yes                |   |

per-treatment analysis.<sup>33</sup> In 4 trials, the loss to follow-up exceeded 20%.<sup>20,35,36,39</sup> Methods of statistical analysis were well described in all but 3 trials.<sup>34,36,41</sup>

TABLE 3 summarizes the quality of evidence for each outcome. 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.

Fifteen studies reported unsatisfactory recovery for corticosteroids and/or antiviral agents.<sup>19-21,23-25,33-35,38-43</sup> Regression analysis revealed a positive inter-

action between corticosteroid and antiviral agent use (OR for interaction term, 0.54 [95% CI, 0.35-0.83];  $P = .004$ ). Corticosteroid therapy alone was associated with reduced risk of unsatisfactory recovery in 10 studies (FIGURE 2 and Table 3).<sup>19,23,34,35,38-43,47</sup> When patients also were treated with antiviral agents, corticosteroids were associated with a further reduction in the risk of unsatisfactory recovery in 2 studies compared with antiviral agents alone.<sup>19,23,47</sup>

Although not effective alone,<sup>19,23,47</sup> antiviral agents were associated with a re-

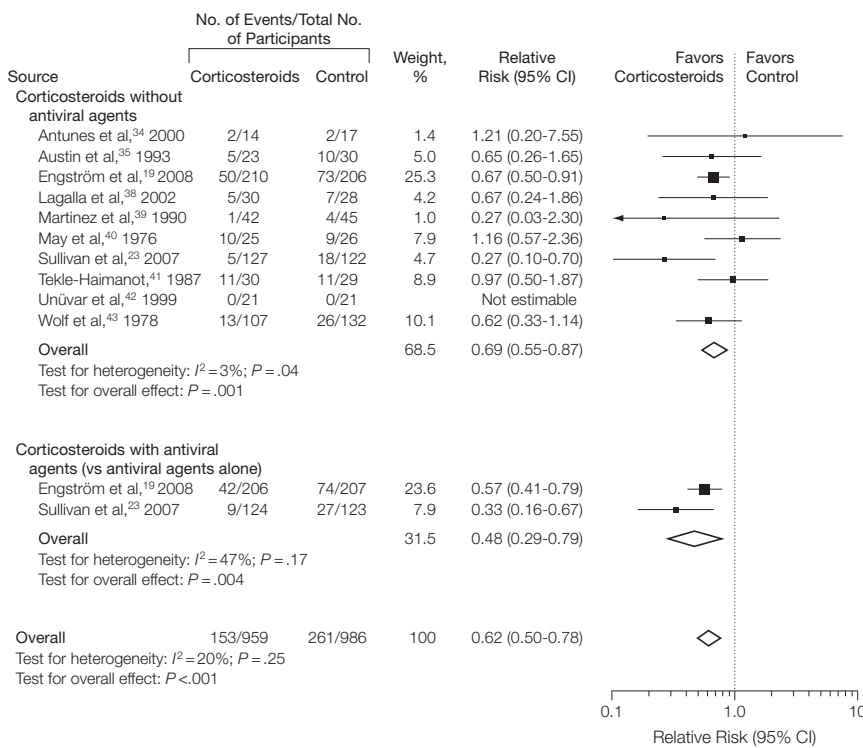
duction in risk of borderline statistical significance when given with corticosteroids compared with corticosteroids alone (FIGURE 3 and Table 3). Eight studies contributed to the pooled estimate.<sup>19-21,23-25,33,34,47</sup> Using a fixed-model analysis, antiviral agents were associated with a significant risk reduction when given in combination with corticosteroids compared with corticosteroids alone (RR, 0.75 [95% CI, 0.59-0.97];  $P = .03$ ;  $I^2 = 10\%$ ;  $P = .36$  for heterogeneity). We found no evidence of publication bias based on visual inspection of funnel plots or Eg-

**Table 3.** Evidence Profile for Corticosteroids and Antiviral Agents in Bell Palsy

| Evidence Profile  |   | RR (95% CI)      | P Value | Risk Without Treatment         | Risk With Treatment (95% CI) | NNTB (95% CI)                     | Quality of Evidence |
|---|---|------------------|---------|--------------------------------|------------------------------|-----------------------------------|---------------------|
| <b>Primary Outcome</b>  |   |                  |         |                                |                              |                                   |                     |
| Unsatisfactory recovery   |   |                  |         |                                |                              |                                   |                     |
| Corticosteroids without antiviral agents                          | No serious methodological limitations, consistent, direct, precise, no publication bias detected                | 0.69 (0.55-0.87) | .001    | 29/100 population <sup>a</sup> | 20 (16-25)/100 population    | 11 (8-25)                         | High <sup>b</sup>   |
| Antiviral agents without corticosteroids                          | No serious methodological limitations, consistent, direct, imprecise, <sup>c</sup> no publication bias detected | 1.14 (0.80-1.62) | .48     | 29/100 population <sup>a</sup> | 33 (23-47)/100 population    | 25 (NNTB 17 to ∞ – NNTH 6)        | Moderate            |
| Corticosteroids with antiviral agents (vs antiviral agents alone) | No serious methodological limitations, inconsistent, <sup>d</sup> direct, precise, no publication bias detected | 0.48 (0.29-0.79) | .004    | 33/100 population <sup>e</sup> | 16 (10-26)/100 population    | 6 (4-14)                          | Moderate            |
| Antiviral agents with corticosteroids (vs corticosteroids alone)  | No serious methodological limitations, inconsistent, <sup>d</sup> direct, precise, no publication bias detected | 0.75 (0.56-1.00) | .05     | 20/100 population <sup>e</sup> | 15 (11-20)/100 population    | 20 (11-∞)                         | Moderate            |
| <b>Secondary Outcomes</b>   |   |                  |         |                                |                              |                                   |                     |
| <b>Corticosteroids</b>  |   |                  |         |                                |                              |                                   |                     |
| Major adverse effects   | No serious methodological limitations, consistent, direct, imprecise, <sup>c</sup> no publication bias detected | 0.56 (0.09-3.39) | .44     | 0/1000 population <sup>f</sup> | 0/1000 population            | NA                                | Moderate            |
| Minor adverse effects   | Serious methodological limitations, <sup>g</sup> consistent, direct, precise, no publication bias detected      | 1.23 (0.93-1.64) | .15     | 9/100 population <sup>f</sup>  | 11 (8-15)/100 population     | NNTH 50 (NNTB 100 to ∞ – NNTH 17) | Moderate            |
| Synkinesis and autonomic dysfunction                              | No serious methodological limitations, consistent, direct, precise, no publication bias detected                | 0.48 (0.36-0.65) | <.001   | 27/100 population <sup>f</sup> | 13 (10-17)/100 population    | 7 (6-10)                          | High <sup>b</sup>   |
| <b>Antiviral agents</b>   |   |                  |         |                                |                              |                                   |                     |
| Major adverse effects   | No serious methodological limitations, consistent, direct, imprecise, <sup>c</sup> no publication bias detected | 0.97 (0.27-3.74) | .67     | 0/1000 population <sup>h</sup> | 0/1000 population            | NA                                | Moderate            |
| Minor adverse effects   | Serious methodological limitations, <sup>g</sup> consistent, direct, precise, no publication bias detected      | 1.02 (0.79-1.33) | .87     | 9/100 population <sup>h</sup>  | 9 (7-12)/100 population      | ∞ (NNTB 50 to ∞ – NNTH 33)        | Moderate            |
| Synkinesis and autonomic dysfunction                              | No serious methodological limitations, consistent, direct, precise, no publication bias detected                | 0.75 (0.51-1.11) | .15     | 27/100 population <sup>h</sup> | 20 (14-30)/100 population    | 14 (NNTB 8 to ∞ – NNTH 33)        | Moderate            |

Abbreviations: CI, confidence interval; NA, not estimable; NNTB, number of patients needed to treat for 1 patient to benefit; NNTH, number of patients needed to treat for 1 patient to be harmed; RR, relative risk.  
<sup>a</sup>Risk is derived from a large observational study describing the natural history of patients not treated for Bell palsy. Unsatisfactory recovery is reported in this study as 29% (overall) and stratified by initial severity of paresis.<sup>3</sup>  
<sup>b</sup>Graded as high and may be upgraded due to strength of effect.  
<sup>c</sup>Quality of evidence downgraded due to a large 95% CI with the possibility of harm.  
<sup>d</sup>Consistency was downgraded for combined therapy because there is a differential effect in combined therapy vs monotherapy.  
<sup>e</sup>The risk of unsatisfactory recovery for corticosteroids alone or antiviral agents alone are the corresponding risks from the lines above.  
<sup>f</sup>Risk was derived from the median control group event rate for each secondary outcome.  
<sup>g</sup>Only 2 studies describe rigorous monitoring of minor adverse effects.  
<sup>h</sup>Risk for those treated with antiviral agents is the same as for those treated with corticosteroids listed above for all secondary outcomes.

**Figure 2.** Unsatisfactory Facial Recovery for Corticosteroids Given With or Without Antiviral Agents



The size of the point estimates indicate the relative weight of each trial in the meta-analysis as determined by the inverse variance method. CI indicates confidence interval.

ger statistics (corticosteroids,  $P=.80$ ; antiviral agents,  $P=.31$ ).

A significant interaction was observed between higher doses ( $\geq 450$  mg) and lower doses ( $< 450$  mg) of corticosteroids (TABLE 4). Corticosteroids were associated with a larger effect at higher doses than at lower doses ( $P=.02$  for interaction). There was no significant interaction in other subgroup analyses. However, a nearly statistically significant difference in effect was observed ( $P=.06$  for interaction) when corticosteroids were used to treat moderate paresis compared with severe paresis.

In the 4 trials that assessed the association of corticosteroids with the outcome of short-term unsatisfactory recovery,<sup>19,23,36,38,47</sup> corticosteroids were associated with a significant benefit (RR, 0.70 [95% CI, 0.55-0.89];  $P=.003$ ;  $I^2=60\%$ ; heterogeneity,  $P=.03$ ). In the 8 trials that assessed the association of

antiviral agents with short-term unsatisfactory recovery, antiviral agents were not associated with a benefit (RR, 0.97 [95% CI, 0.84-1.12];  $P=.69$ ;  $I^2=19\%$ ; heterogeneity,  $P=.26$ ).<sup>19-23,25,33,34,47</sup>

Meta-analysis of 3 studies showed a RR reduction in synkinesis and autonomic dysfunction in patients treated with corticosteroids (Table 3).<sup>19,38,43</sup> Meta-analysis of 2 trials showed no reduction in synkinesis and autonomic dysfunction among patients treated with antiviral agents.<sup>19,33</sup>

Few major adverse effects were associated with corticosteroid or antiviral agent treatment in the 9 trials that reported this outcome.\* Eight major adverse effects were reported in 2122 patients. Three deaths were reported (all of which occurred in 1 trial)<sup>23</sup>; 2 of these deaths occurred in the double placebo group and 1 in the combined antiviral

\*References 19, 20, 22, 23, 35, 38, 39, 42, 43.

agent and placebo group. None were attributed to treatment. One episode of recurrent atrial fibrillation was described in a patient receiving antiviral agents.<sup>19</sup> In one trial, 4 patients receiving corticosteroids developed gastric ulceration.<sup>22</sup> Avascular necrosis of the hip was not reported in any studies. Neither corticosteroids nor antiviral agents were associated with an increased risk of major adverse effects compared with control groups (Table 3).

In the 7 corticosteroid trials that reported minor adverse effects,<sup>19,23,35,38,39,42,43</sup> there was no apparent association with an increase in the risk of minor adverse effects (Table 3). Four trials reported minor adverse effects for antiviral agents.<sup>19,20,22,23</sup> There was no apparent association with an increase in the risk of adverse effects in patients taking antiviral agents. Only 2 studies described rigorous monitoring methods for minor adverse effects.<sup>19,23</sup>

**COMMENT**

Recent evidence from large RCTs indicates that Bell palsy may best be managed with corticosteroids and that antiviral agents may be of no benefit. This systematic review has shown a possible incremental benefit of adding antiviral agents to corticosteroid therapy and a synergistic effect when these 2 agents are given in combination.

Based on the GRADE criteria,<sup>27</sup> high-quality evidence suggests that corticosteroids alone reduce the risk of unsatisfactory recovery by 9% in absolute terms, with a NNTB of 11 (95% CI, 8-25). Corticosteroid therapy combined with antiviral agents reduced the risk of unsatisfactory recovery compared with antiviral agents alone. Corticosteroids were also associated with a 14% absolute risk reduction of synkinesis and autonomic dysfunction (NNTB, 7; 95% CI, 6-10) (moderate quality of evidence). Corticosteroids were not associated with an increased risk of adverse effects.

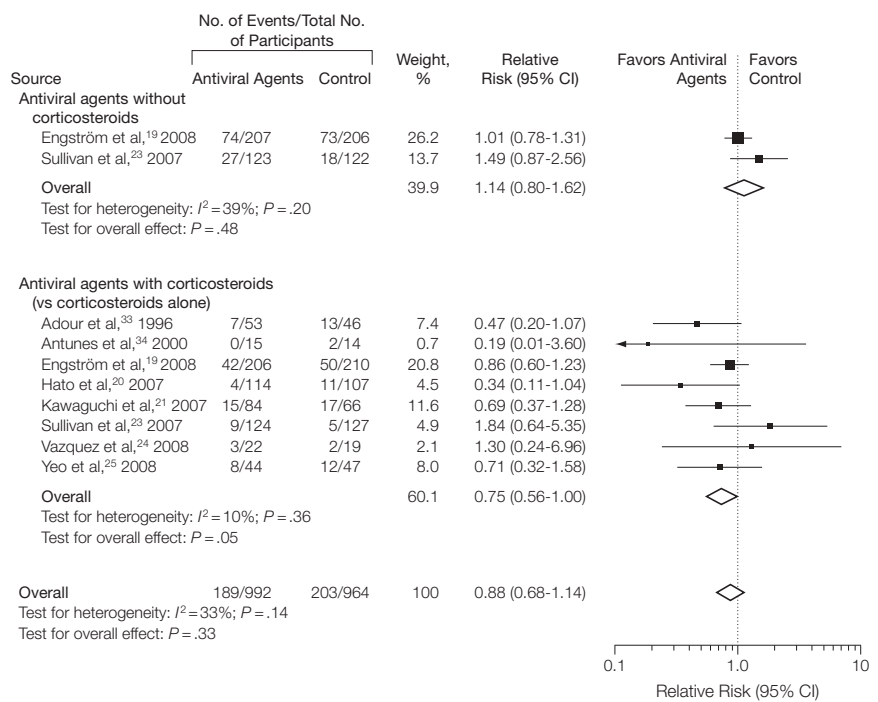
Moderate-quality evidence suggests that antiviral agents given without corticosteroids were not associated with benefit. However, antiviral agents com-

bined with corticosteroids are associated with reduced risk of unsatisfactory recovery (of borderline significance) compared with corticosteroids alone.

Corticosteroids and antiviral agents appear to be associated with larger effects when administered together than when given separately. We view this apparent difference in effect as credible but not definitive.<sup>49</sup> The conclusion is based on 1 of 5 a priori hypotheses with a specified direction. Some of the results come from within-study comparisons<sup>19,23</sup>; the effect is not likely to be due to chance, is relatively large, has biological plausibility, and is consistent across studies.

Corticosteroids were associated with greater benefit when prescribed at doses of greater than 450 mg compared with doses lower than 450 mg. This subgroup effect has limited credibility because it is based on between-study comparisons, has not been supported by external evidence, and is inconsistent among studies. Furthermore, the lower dose subgroup effect is based on small studies with meth-

**Figure 3.** Unsatisfactory Facial Recovery for Antiviral Agents Given With or Without Corticosteroids



The size of the point estimates indicate the relative weight of each trial in the meta-analysis as determined by the inverse variance method. CI indicates confidence interval.

**Table 4.** Subgroup Analysis of Unsatisfactory Facial Recovery After Treatment With Corticosteroids and Antiviral Agents

| Subgroup                      | No. of Studies  | No. of Patients With Unsatisfactory Recovery/Total |         | RR (95% CI) | I <sup>2</sup> , % | P Value <sup>a</sup> | P Value for Interaction Between Subgroups <sup>b</sup> |
|-------------------------------|-----------------|--|---------|-------------|--------------------|----------------------|--|
|                               |                 | Treatment  | Control |             |                    |                      |  |
| <b>Corticosteroids</b>        |                 |  |         |             |                    |                      |  |
| Initial severity <sup>c</sup> | Moderate        | 3 <sup>23,39,40,48</sup>                           | 9/210   | 28/188      | 0.31 (0.15-0.63)   | 0                    | .06  |
|                               | Severe          | 4 <sup>23,39-41,48</sup>                           | 16/103  | 29/129      | 0.87 (0.40-1.92)   | 49                   |  |
| Dose <sup>d</sup>             | <450 mg         | 4 <sup>34,35,40,41</sup>                           | 28/92   | 32/102      | 0.96 (0.63-1.46)   | 0                    | .02  |
|                               | ≥450 mg         | 6 <sup>19,23,38,39,42,43</sup>                     | 125/867 | 229/884     | 0.56 (0.46-0.70)   | 8                    |  |
| Time to treatment             | Within 72 h     | 5 <sup>19,23,38,40,42</sup>                        | 121/743 | 208/733     | 0.58 (0.42-0.80)   | 47                   | .38  |
|                               | Not within 72 h | 5 <sup>34,35,39,41,43</sup>                        | 32/216  | 53/253      | 0.73 (0.49-1.08)   | 0                    |  |
| Blinding                      | Blinded         | 6 <sup>19,23,34,35,38,40</sup>                     | 128/759 | 220/759     | 0.60 (0.46-0.78)   | 31                   | .45  |
|                               | Not blinded     | 4 <sup>39,41-43</sup>                              | 25/200  | 41/227      | 0.73 (0.47-1.13)   | 0                    |  |
| <b>Antiviral agents</b>       |                 |  |         |             |                    |                      |  |
| Initial severity <sup>c</sup> | Moderate        | 3 <sup>20,23,33,48</sup>                           | 20/231  | 19/216      | 0.83 (0.30-2.28)   | 50                   | .91  |
|                               | Severe          | 3 <sup>20,23,33,48</sup>                           | 26/164  | 28/159      | 0.76 (0.26-2.22)   | 78                   |  |
| Dose <sup>e</sup>             | Low dose        | 7 <sup>20,21,23-25,33,34</sup>                     | 73/579  | 80/548      | 0.81 (0.52-1.25)   | 44                   | .52  |
|                               | High dose       | 1 <sup>19</sup>                                    | 116/413 | 123/416     | 0.95 (0.77-1.18)   | 0                    |  |
| Time to treatment             | Within 72 h     | 4 <sup>19,23,25,33</sup>                           | 162/735 | 161/730     | 1.00 (0.76-1.31)   | 32                   | .06  |
|                               | Not within 72 h | 4 <sup>20,21,25,34</sup>                           | 27/257  | 42/234      | 0.61 (0.39-0.94)   | 0                    |  |
| Blinding                      | Blinded         | 6 <sup>19,23-25,33,34</sup>                        | 170/794 | 175/791     | 0.96 (0.75-1.23)   | 24                   | .09  |
|                               | Not blinded     | 2 <sup>20,21</sup>                                 | 19/198  | 28/173      | 0.57 (0.30-1.07)   | 18                   |  |

Abbreviations: CI, confidence interval; RR, relative risk.

<sup>a</sup>Based on the  $\chi^2$  test.

<sup>b</sup>Based on z scores.

<sup>c</sup>Subgroup analysis contains within and between study level data. All patients not accounted for because subgroup data not available for every patient. Severity is defined by primary author. See eTable (available at <http://www.jama.com>) for further details.

<sup>d</sup>Dose is in an equivalent to prednisone.

<sup>e</sup>Low dose is suitable for treatment of herpes simplex virus, high dose is suitable for treatment of varicella zoster virus.

odological limitations while the higher dose subgroup is based on larger more rigorous studies.

Patients with complete or severe initial paresis have a poorer prognosis than those with incomplete paresis.<sup>2</sup> Our results suggest that corticosteroids are associated with a smaller benefit in patients with severe than in those with moderate severity pareses, however the test for interaction was not statistically significant. The effect was substantial, in the predicted direction (1 of 5 a priori hypotheses), and was based primarily on within-study comparisons. However, results were inconsistent across studies.

We found no difference in the effect of corticosteroids on unsatisfactory recovery when patients are treated within 72 hours vs later. This finding was the result of between-study comparisons of studies that restricted enrollment to those presenting within 72 hours vs those that enrolled patients presenting both before and after 72 hours of onset. Thus, the subgroup analysis is weak. If time to treatment data were available for individual patients, a more powerful analysis would be possible.

The etiologic basis for Bell palsy may be due not only to reactivation of herpes simplex virus, but also due to reactivation of VZV.<sup>12</sup> Adequate treatment of VZV requires a higher dose of antiviral agents.<sup>12</sup> We did not find improved facial recovery in patients treated with higher doses of antiviral agents, although only 1 study used a dose appropriate for treatment of VZV.<sup>19</sup>

Our meta-analysis has limitations. First, 2 trials<sup>19,23</sup> contributed almost half of the patients in the meta-analysis. In this review, however, results were consistent across multiple studies. We also chose a random-effects model which, although it gives a higher weight to large studies, it has a lower large to small study gradient in weight than fixed-effects models if there is variation between studies. Second, our meta-analysis may be underpowered for some outcomes such as minor adverse effects of corticosteroids and synkinesis

and autonomic dysfunction for antiviral agents. These associations had substantial, but nonsignificant treatment effects. Third, included studies were not blinded by author or journal source. Given reviewer familiarity with the literature, complete anonymity would be difficult to achieve. However, we used criteria delineated by the Cochrane group<sup>26</sup> to assess methodological quality. Fourth, our primary outcome is subjective and susceptible to biased assessment, particularly in nonblinded studies. However, blinded and nonblinded studies showed similar results. Finally, there was considerable heterogeneity in the instruments used to measure outcomes. One study, however, showed moderate to good agreement (chance-corrected agreement of 0.65 on a scale from 0 to 1.0) between 3 of the grading systems used in this review (Sunnybrook, House Brackmann, Yanagihara).<sup>50</sup> Our results were consistent across studies with different measurement instruments.

A recent study suggested that corticosteroid monotherapy may be more cost-effective than combining antiviral agents and corticosteroids.<sup>51</sup> This analysis was based on trial results that did not demonstrate a synergistic effect of corticosteroids and antiviral agents.<sup>23</sup> Our results suggest a possible incremental benefit of antiviral agents in addition to corticosteroids, with an absolute risk reduction of 5% compared with corticosteroids alone. This effect, however, is not definitive and did not quite reach statistical significance. Moreover, 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. Further primary studies are needed to definitively establish—or refute—an incremental benefit of combined therapy compared with corticosteroid monotherapy.

**Author Contributions:** Dr de Almeida had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** de Almeida, Al Khabori, Guyatt, Witterick, Lin, Nedzelski, Chen.

**Acquisition of data:** de Almeida, Al Khabori.

**Analysis and interpretation of data:** de Almeida, Al Khabori, Guyatt, Witterick, Lin, Nedzelski, Chen.

**Drafting of the manuscript:** de Almeida, Guyatt, Chen.

**Critical revision of the manuscript for important intellectual content:** de Almeida, Al Khabori, Guyatt, Witterick, Lin, Nedzelski, Chen.

**Statistical analysis:** de Almeida, Al Khabori, Guyatt.

**Administrative, technical, or material support:** Guyatt, Witterick, Lin, Nedzelski, Chen.

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