

# Evidence-based guideline update: Steroids and antivirals for Bell palsy

Report of the Guideline Development Subcommittee of the American Academy of Neurology



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## ABSTRACT

**Objective:** To review evidence published since the 2001 American Academy of Neurology (AAN) practice parameter regarding the effectiveness, safety, and tolerability of steroids and antiviral agents for Bell palsy.

**Methods:** We searched Medline and the Cochrane Database of Controlled Clinical Trials for studies published since January 2000 that compared facial functional outcomes in patients with Bell palsy receiving steroids/antivirals with patients not receiving these medications. We graded each study (Class I–IV) using the AAN therapeutic classification of evidence scheme. We compared the proportion of patients recovering facial function in the treated group with the proportion of patients recovering facial function in the control group.

**Results:** Nine studies published since June 2000 on patients with Bell palsy receiving steroids/antiviral agents were identified. Two of these studies were rated Class I because of high methodologic quality.

**Conclusions and Recommendations:** For patients with new-onset Bell palsy, steroids are highly likely to be effective and should be offered to increase the probability of recovery of facial nerve function (2 Class I studies, Level A) (risk difference 12.8%–15%). For patients with new-onset Bell palsy, antiviral agents in combination with steroids do not increase the probability of facial functional recovery by >7%. Because of the possibility of a modest increase in recovery, patients might be offered antivirals (in addition to steroids) (Level C). Patients offered antivirals should be counseled that a benefit from antivirals has not been established, and, if there is a benefit, it is likely that it is modest at best. *Neurology*® 2012;79:2209–2213

## GLOSSARY

**AAN** = American Academy of Neurology; **AE** = adverse event; **CI** = confidence interval; **NNT** = number needed to treat; **RD** = risk difference.

Bell palsy is an acute, peripheral facial paresis of unknown cause.<sup>1</sup> Usually the diagnosis is established without difficulty.<sup>2</sup> Up to 30% of patients with Bell palsy fail to recover facial function completely.<sup>3</sup> The disease is common, with an annual incidence of 20 per 100,000. Thus, thousands of patients with Bell palsy are left with permanent, potentially disfiguring facial weakness each year.

In 2001, the Quality Standards Subcommittee of the American Academy of Neurology (AAN) published an evidence-based practice guideline for the treatment of Bell palsy.<sup>4</sup> The 2001 guideline concluded that steroids were probably effective and antivirals (acyclovir) possibly effective in increasing the probability of complete facial functional recovery in patients with Bell palsy.

This update, developed by the AAN Guideline Development Subcommittee (see appendices e-1 and e-2 on the *Neurology*® Web site at [www.neurology.org](http://www.neurology.org)), systematically reviews studies published since June 2000 that are considered relevant to this question: For patients with new-onset Bell palsy, does treatment with steroids or antiviral agents (acyclovir, famciclovir, valacyclovir) improve facial functional recovery?

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Supplemental Data



Podcast



From the Department of Neurology, University of Kansas Medical Center, Kansas City.

Approved by the Guideline Development Subcommittee on January 21, 2012; by the Practice Committee on May 14, 2012; and by the AAN Board of Directors on August 21, 2012.

**Study funding:** This guideline was developed with financial support from the American Academy of Neurology. None of the authors received reimbursement, honoraria, or stipends for their participation in development of this guideline.

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**DESCRIPTION OF THE ANALYTIC PROCESS** We searched Medline for articles published from June 2000 through January 2012 using the term “Bell’s palsy” and the sensitive, therapeutic clinical filter<sup>5</sup> (see appendix e-3 for the specific search strategy employed). The Cochrane Database of Systematic Reviews and Controlled Clinical Trials was also searched. A secondary search of the references of selected articles and review articles (including Cochrane systematic reviews) was performed to identify studies missed by our search strategy.

The titles and abstracts of the identified citations were reviewed for relevance to the clinical question. The full text of potentially relevant articles was retrieved and included in the analysis if these studies determined facial functional outcomes after at least 3 months of follow-up in at least 20 patients with new-onset Bell palsy. We included only controlled trials with prospective data collection comparing outcomes in patients treated with steroids or antiviral agents with patients not treated with these medications. Both authors independently reviewed articles and completed data abstraction. Discrepancies were resolved through discussion.

Facial functional recovery was defined as “good” or “complete” using the same criteria used in the 2001 practice guideline. The quantitative measure of the treatment effect employed was the difference in the proportion of patients attaining complete or good facial recovery in the treatment group relative to the comparative group (i.e., the risk difference [RD]). In studies using the House and Brackmann<sup>6</sup> facial function scoring system, we considered an outcome of grade I or II a good recovery. When comparing the proportion of patients recovering complete facial function, we considered an outcome of

grade I a complete recovery. The measure of statistical precision used was the 95% confidence intervals (CIs) of the RD, and an RD  $\geq 10\%$  was considered clinically meaningful. The frequency and severity of the adverse events (AEs) from the treatments employed were also abstracted.

Studies were rated for their risk of bias using the AAN 4-tiered classification of evidence scheme for therapeutic studies (appendix e-4). Studies from the original guideline were re-rated using the updated classification of evidence scheme. The strength of practice recommendations was linked to the strength of evidence (appendix e-5).

For the purpose of formulating conclusions and recommendations, we used the term “steroids” regardless of the specific type, dose, and route of steroids used in the reviewed studies. Likewise, we used the term “antiviral agents” regardless of the specific type of agent used in the reviewed studies.

**ANALYSIS OF EVIDENCE** Our search strategy identified 340 citations. We reviewed the full text of 38 potentially relevant articles. Nine articles<sup>7–15</sup> fulfilled the inclusion criteria.

**For patients with new-onset Bell palsy, does treatment with steroids improve facial functional recovery?** The search strategy identified 3 articles<sup>8,11,15</sup> published since the initial review comparing outcomes in patients with Bell palsy treated with steroids with those not treated with steroids. Table 1 summarizes these studies and includes 2 of the studies reviewed in the original guideline that attained a grading of Class II or better.<sup>16,17</sup> Only Class I and Class II studies are discussed further.

**Table 1** Design characteristics and outcomes in Class I and Class II controlled studies of patients with Bell palsy treated with antiviral agents and steroids relative to patients treated with steroids alone

Author and year	Cohort size	Age, y	Steroid dose duration Rx	Severity, % <sup>a</sup>	Duration, d <sup>b</sup>	Follow-up, mo	Completion rate, % <sup>c</sup>	Blind	Class	NH % <sup>d</sup>	RD good recovery (CI)	RD complete recovery (CI)
Engström <sup>8</sup> 2008	422	Median 39 (IQR 23–54)	Prednisolone <sup>e</sup> 60 mg daily $\times$ 5, taper	Med HB 4 IQR 3–5	3	12	99	Yes	I	56	—	15% (8%–21%)
Sullivan <sup>11</sup> 2007	551	Mean 44 (16.4 SD)	Prednisolone 25 mg BID	Mean HB 3.6 $\pm$ 1.3	3	9	90	Yes	I	82	—	12.8% (7.2%–18.6%)
Lagalla <sup>15</sup> 2002	58	Range 15–84	Prednisone 1 g IV $\times$ 3 d then 0.5 g IV $\times$ 3 d	24	3	12	100	Yes	II	75	7% (–14% to 27%)	—
May <sup>16</sup> 1976	51	53% $>$ 30	Prednisone 410 mg 10 d	47	2	6	100	Yes	II <sup>f</sup>	81	–0.75% (–18% to 22.5%)	—
Taverner <sup>17</sup> 1954	26	Mean 40 (range 12–76)	Hydrocortisone 1 g 8 d	23	9	NS	100	Yes	II <sup>f</sup>	67	5.25% (–27% to 55%)	—

Abbreviations: CI = 95% confidence interval; HB = House Brackmann score; IQR = interquartile range; NH = natural history; NS = not stated; RD = risk difference (positive values results favoring steroids).

<sup>a</sup>Percentage of patients with complete palsy.

<sup>b</sup>Maximum duration of palsy before steroids started.

<sup>c</sup>Percentage of subjects followed to study completion.

<sup>d</sup>Percentage of patients not treated with steroids who attained a good outcome.

<sup>e</sup>Prednisolone and prednisone are dose-equivalent steroids.

<sup>f</sup>Downgraded by one Class from the rating in the original practice parameter because of no description of allocation concealment.

The 2 Class I studies<sup>8,11</sup> randomized patients to steroids vs placebo and described concealed allocation. Both studies enrolled patients within 3 days of the onset of facial weakness. Both studies used prednisolone, one at 60 mg/d for 5 days followed by a 5-day taper,<sup>8</sup> the other 25 mg BID for 10 days.<sup>11</sup> All studies employed masked outcome assessment and had high rates of follow-up.

The 3 Class II studies<sup>15–17</sup> did not describe concealed allocation. These studies enrolled fewer than 100 patients each and described complete follow-up and masked outcome assessment. One of the Class II<sup>15</sup> studies used IV prednisone. The other 2 used oral steroid preparations.

**Efficacy.** The 2 Class I studies demonstrated a significant increase in the probability of complete recovery in patients randomized to steroids (RD favoring steroids 12.8% and 15%), translating to a number needed to treat (NNT) of 6 to 8. None of the Class II studies demonstrated a significant benefit from steroids. However, these studies lacked the statistical precision to exclude a clinically meaningful effect of steroids.

**Safety and tolerability.** All studies reported AEs from steroids. In general, these were minor and temporary. The most common AEs reported were insomnia and dyspepsia.

**Conclusion.** For patients with new-onset Bell palsy, it is highly likely that steroids are effective in increasing the probability of complete facial functional recovery (NNT 6–8, 2 Class I studies).

**For patients with new-onset Bell palsy, does treatment with antiviral agents improve facial functional recovery?** We found 8 articles<sup>7–14</sup> published since 2000 comparing outcomes in patients with new-onset Bell palsy treated with antiviral agents. Five of these studies<sup>7,9,12–14</sup> were rated Class IV because of nonindependent, nonmasked, non-objective outcome assessment. These studies are not discussed further. Table 2 summarizes the remaining Class I and II studies (2 Class I, 1 Class II).<sup>8,10,11</sup> The table also

includes the single Class II study<sup>18</sup> from the original guideline.

The Class I studies compared outcomes in patients randomized to antivirals and placebo. In addition, the Class I studies compared outcomes in patients on antivirals plus steroids with patients on steroids alone. The Class II studies<sup>10,18</sup> compared outcomes only of patients on antivirals plus steroids with patients on steroids alone.

Valacyclovir was used in one study<sup>8</sup> whereas acyclovir was the antiviral agent employed in the other studies. The doses are indicated in table 2. The majority of patients were enrolled within 3 days of onset of facial weakness.

**Efficacy.** None of the Class I studies demonstrated a significant improvement with the use of antivirals as compared with placebo (random-effects Mantel-Haenszel pooled RD 4% favoring placebo, 95% CI –3% to 11%). Although a benefit of antivirals was not observed in comparison with placebo, some authors have suggested antivirals might have an additional benefit when added to steroids.<sup>9</sup>

All of the studies reviewed here specifically compared outcomes in patients on steroids and antivirals with patients on steroids alone (table 2). No significant benefit of antivirals added to steroids as compared with steroids alone was observed in the Class I and II studies. However, the 95% CIs of the Class I studies indicate that the studies' statistical precision was insufficient to exclude a modest benefit or harm of antivirals added to steroids (random-effects Mantel-Haenszel pooled RD 0, 95% CI –8% favoring steroids alone to 7% favoring antivirals plus steroids). Adding the Class II studies to the meta-analysis fails to importantly increase the precision of the analysis (pooled RD 4% favoring steroids plus antivirals, 95% CI –4% to 12%).

**Safety and tolerability.** None of the studies demonstrated a significant increase in any AE for patients randomized to an antiviral agent.

**Table 2** Design characteristics and outcomes in Class I and II controlled studies of patients with Bell palsy treated with antiviral agents and steroids relative to patients treated with steroids alone

Author and year	Cohort size	Age, y (range)	Dose duration Rx	Severity, % <sup>a</sup>	Duration d <sup>b</sup>	Follow-up, mo	Completion rate, % <sup>c</sup>	Blind	Class	NH % <sup>d</sup>	RD complete recovery (CI)
Engström <sup>8</sup> 2008	829	Median 39 (IQR 23–54)	VC 3000 mg/day 7 days	Med HB 4 IQR 3–5	3	12	99	Yes	I	76	3.4% (–4.6–11.3%)
Sullivan <sup>11</sup> 2007	551	Mean 44 (16.4 SD)	AC 2000 mg/day 10 days	Mean HB 3.6 ± 1.3	3	9	90	Yes	I	93	–3.3% (–9.7–2.7%)
Yeo <sup>10</sup> 2008	91	Mean 41 (1.7 SD)	AC 1000 mg/d 5 days	23	53% ≤ 3 d	6	100	Yes	II	85	8.1% (–5.6–21.6%)
Adour <sup>18</sup> 1996	99	Mean 43	AC 400 mg × 5 qd 10 days	20	3	12	83	Yes	II	72	15% (–0.9–30.8%)

Abbreviations: AC = acyclovir; CI = 95% confidence interval; HB = House Brackmann score; IQR = interquartile range; RD = risk difference (positive values results favoring antivirals); NH = natural history; VC = valacyclovir.

<sup>a</sup>Percentage of patients with complete palsy.

<sup>b</sup>Maximum duration of palsy before steroids started.

<sup>c</sup>Percentage of subjects followed to study completion.

<sup>d</sup>Percentage of patients treated with steroids only who attained a good outcome.

**Conclusion.** For patients with acute-onset Bell palsy, it is highly likely that antivirals do not moderately (RD >7%) increase the likelihood of improved facial functional recovery (2 Class I studies). The pooled results of studies with a low risk of bias lack the statistical precision to exclude a modest benefit (RD favoring antivirals ≤7%) or modest harm (RD favoring steroids alone ≤8%).

**RECOMMENDATIONS** For patients with new-onset Bell palsy, oral steroids should be offered to increase the probability of recovery of facial nerve function (Level A).

For patients with new-onset Bell palsy, antivirals (in addition to steroids) might be offered to increase the probability of recovery of facial function (Level C). Patients offered antivirals should be counseled that a benefit from antivirals has not been established, and, if there is a benefit, it is likely that it is modest at best (RD <7%).

**PUTTING THE EVIDENCE INTO A CLINICAL CONTEXT** Although there is strong evidence that steroid use increases the probability of good facial functional recovery in patients with Bell palsy, it does not necessarily follow that all patients with Bell palsy need to take steroids. For example, it would be reasonable for a clinician to opt not to use steroids in a patient with brittle diabetes mellitus. Other comorbidities potentially requiring further consideration include morbid obesity, osteopenia, and a prior history of steroid intolerance.

We found limited evidence of the efficacy of steroids and antivirals in important Bell palsy subgroups, including those with a lower probability of recovery because of severe palsy at presentation and those with possible zoster sine herpette. Such studies are particularly important relative to the efficacy of the addition of antivirals to steroids given the lack of evidence for moderate efficacy in the “typical” patient with Bell palsy.

Authors of one Class I study<sup>8</sup> performed a preplanned subgroup analysis on patients with severe palsy at presentation<sup>19</sup> defined by a Sunnybrook Scale score of 0 to 25. This analysis showed no significant difference in 12-month recovery rates between patients treated with prednisolone alone as compared with patients treated with prednisolone plus valacyclovir (RD 0.2% favoring valacyclovir 95% CI, -18% to 17.6%). However, the analysis lacked the statistical precision to exclude an important beneficial effect (or harm) from the addition of valacyclovir. A Class IV study<sup>9</sup> observed a significant improvement in recovery (RD 26.6%) between patients with severe Bell palsy treated with prednisone alone and patients with severe Bell palsy treated with prednisone plus famciclovir (House-Brackmann Scale score of 5 or 6). This study had a high risk of bias because of pseudo-randomized treatment allocation and unmasked outcome assessment.

Relative to zoster sine herpette, a Class IV study<sup>12</sup> observed no significant difference in recovery after

treatment with prednisolone alone as compared with treatment with prednisolone plus valacyclovir in a subgroup of 28 patients with evidence of zoster reactivation (hazard ratio for recovery 1.6 favoring prednisolone plus valacyclovir, 95% CI 0.4 to 6.1). The small sample size and high risk of bias make this observation inconclusive.

These studies in aggregate do not provide strong evidence to identify subgroups of patients that might benefit more or less from treatment.

Because the studies included only patients presenting early after palsy onset, it is difficult to determine the effect of steroid or antiviral treatment in patients presenting later in the course of their illness (e.g., 1 week after the onset of facial weakness). Likewise, although it seems reasonable to assume that an equivalent dose of alternative steroids would also be effective, decisions regarding alternative steroid dosing regimens necessarily require clinician judgment.

**RECOMMENDATIONS FOR FUTURE RESEARCH** It is unlikely that additional research regarding the efficacy of steroids will change the current estimate of its effect. Large randomized trials comparing outcomes in patients with Bell palsy receiving steroids with or without antivirals would help in determining whether the addition of antivirals to steroid treatment results in a modest benefit. Such trials should be powered to allow prespecified subgroup analyses of patients with a poorer prognosis and of patients with possible zoster sine herpette. Further future research efforts should be directed toward finding the optimal dose and timing of steroids, the effect of other therapeutic modalities, and the identification of the effect of steroids in specific populations, such as in children.

#### AUTHOR CONTRIBUTIONS

G. Gronseth: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis, study supervision. R. Paduga: drafting/revising the manuscript, acquisition of data.

#### DISCLOSURE

G. Gronseth serves as an editorial advisory board member of *Neurology Now*; served on a speakers' bureau for Boehringer Ingelheim; and receives honoraria from Boehringer Ingelheim and the American Academy of Neurology. R. Paduga reports no disclosures. **Go to [Neurology.org](http://Neurology.org) for full disclosures.**

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Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology* peer reviewers and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at [www.aan.com](http://www.aan.com).

Received May 15, 2012. Accepted in final form August 21, 2012.

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*Neurology* 2012;79;2209-2213 Published Online before print November 7, 2012

DOI 10.1212/WNL.0b013e318275978c

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