GUIDELINE SYNTHESIS

Pharmacologic Interventions for Bell's Palsy

Guidelines Being Compared:

1 American Academy of Neurology (Am Acad Neurol)

Evidence-based guideline update: steroids and antivirals for Bell palsy: report of the Guideline Development Subcommittee of the American Academy of Neurology.

2012 Nov 01

View Summary >

2 American Academy of Otolaryngology - Head and Neck Surgery Foundation (AAO-HNSF)

Clinical practice guideline: Bell's palsy.

2013 Nov 01

View Summary >

Areas of Agreement and Difference

A direct comparison of recommendations presented in the above guidelines for the use of medications in the management of Bell's palsy is provided in the tables below. The AAO-HNSF guideline addresses non-pharmacologic aspects of management of Bell's palsy, including laboratory testing, diagnostic imaging, and eye care. These topics, however, are beyond the scope of this synthesis.

AAN and AAO-HNSF are in agreement that oral steroids are recommended for new-onset Bell's palsy patients to increase the probability of recovery of facial nerve function. Both developers make the strongest possible recommendation according to their respective grading schemes.

AAO-HNSF specifies that steroids should be prescribed within 72 hours of symptom onset for patients 16 years and older. AAN does not cite a specific timeframe in its recommendation, but is in agreement that steroids should be initiated as soon as possible. The developer notes that, because the evidence considered during guideline development 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., one week after the onset of facial weakness).

The groups further agree that oral steroids may not be appropriate in certain individuals presenting with Bell's palsy, including morbidly obese patients and patients with diabetes mellitus or a history of steroid intolerance.

Antiviral Therapy

Neither group recommends the use of oral antiviral therapy alone for new-onset Bell's palsy, with AAO-HNSF making a "Strong" recommendation against it. Both developers do, however, acknowledge that the evidence appears to demonstrate a small potential benefit associated with the use of antivirals ***in addition to*** oral steroid therapy. AAN makes a "Level C" (possibly effective, ineffective or harmful) recommendation to that effect, noting that patients should be counseled that a benefit from antivirals has not been established and, if there is a benefit, it is likely modest at best.

Similarly, AAO-HNSF classifies its evidence-based statement that clinicians may offer oral antiviral therapy in addition to oral steroids within 72 hours for patients with Bell's palsy as an "Option" (i.e., either the quality of evidence that exists is suspect or well-done studies show little clear advantage to one approach vs. another).

Areas of Difference

Comparison of Recommendations

Pharmacologic Interventions for Bell's Palsy

AAN (2012)	**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 (risk difference [RD] <7%). **Putting the Evidence into 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. The authors 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 herpete. 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 performed a preplanned subgroup analysis on patients with severe palsy at presentation defined by a Sunnybrook Scale score

	patients treated with prednisolone plus valacyclovir (RD 0.2% favoring valacyclovir 95% confidence intervals [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 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 pseudorandomized treatment allocation and unmasked outcome assessment. Relative to zoster sine herpete, a Class IV study 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., one 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.
AAO-HNSF (2013)	**Oral Steroids** Clinicians should prescribe oral steroids within 72 hours of symptom onset for Bell's palsy patients 16 years and older.

Action Statement Profile

- Aggregate evidence quality: **Grade A**
- Level of confidence in evidence: High
- Benefit: Improvement in facial nerve function, faster recovery
- Risks, harms, costs: Steroid side effects, cost of therapy
- Benefit-harm assessment: Preponderance of benefit
- Value judgments: None
- Intentional vagueness: None
- Role of patient preferences: Small
- Exceptions: Diabetes, morbid obesity, previous steroid intolerance, and psychiatric disorders. Pregnant women should be treated on an individualized basis
- Policy level: **Strong recommendation**
- Differences of opinion: None

Supporting Text

The purpose of this statement is to encourage the use of oral corticosteroids for patients 16 years and older with new-onset Bell's palsy. Goals of treatment for Bell's palsy patients include decreasing recovery time and improving facial nerve functional recovery.

Inflammation and edema causing compression of the facial nerve as it travels through the fallopian (facial) canal is the leading posited mechanism of Bell's palsy. Potent anti-inflammatory agents, such as oral corticosteroids, target the inflammatory process, presumably decreasing nerve edema and thereby facilitating the return of facial nerve function.

An evidence-based practice parameter developed by the AAN recently evaluated the efficacy of oral corticosteroids and acyclovir in patients with Bell's palsy. Based on the results of 2 randomized clinical trials with objective outcomes, the AAN concluded that "steroids are highly likely to be effective and should be

The study by Sullivan et al., a double-blind, placebo-controlled, randomized, factorial trial involving 551 patients, reported significant improvement of facial nerve function in patients treated with prednisolone within 72 hours of onset. Participants in the study were randomly assigned to groups treated with prednisolone, acyclovir, placebo, or both active agents. All participants were treated for 10 days, and all patients were 16 years of age and older. Sullivan et al. reported that 83% of the participants randomized to prednisolone had recovered facial nerve function 3 months after treatment compared with 63.6% of those randomized to placebo (*P <.001*). Evaluation 9 months posttreatment revealed 94.4% recovery in the prednisolone group and 81.6% recovery in the placebo group.

The study by Engstrom et al. was a similarly randomized, double-blind, placebo-controlled, multicenter trial involving 829 patients (ages 18-75 years). This trial compared the short- and long-term effects of prednisolone and valacyclovir in facial nerve recovery attributed to Bell's palsy. Individuals within 72 hours of initial diagnosis were randomized to placebo-plus-placebo, prednisolone-plus-placebo, valacyclovir-plus-placebo, or prednisolone-plus-valacyclovir groups. Statistically significant shorter times to recovery were noted in the 416 patients treated with prednisolone compared with the 413 patients who did not receive prednisolone.

Both of the randomized clinical trials with objective outcomes above used prednisolone for a 10-day course. One used prednisolone 25 mg twice daily for 10 days, and the other used 60 mg per day for 5 days, then tapered over 5 days. Based on these studies, the GDG recommends a 10-day course of oral steroids with at least 5 days at a high dose (either prednisolone 50 mg for 10 days or prednisone 60 mg for 5 days with a 5-day taper) initiated within 72 hours of symptom onset. The benefit of treatment after 72 hours is less clear.

Use of Steroids in Children with Bell's Palsy

as the generally favorable benefit-harm ratio of steroid therapy, oral steroids may be considered in pediatric patients with a large role for caregiver involvement in the decision-making process.

Antiviral Monotherapy

Clinicians should not prescribe oral antiviral therapy alone for patients with new-onset Bell's palsy.

Strong recommendation (against) based on high-quality randomized controlled trials with a preponderance of benefit over harm.

Action Statement Profile

- Aggregate evidence quality: **Grade A**
- Level of confidence in evidence: High
- Benefit: Avoidance of medication side effects, cost savings
- Risks, harms, costs: None
- Benefit-harm assessment: Preponderance of benefit
- Value judgments: None
- Intentional vagueness: None
- Role of patient preferences: Small
- Exceptions: None
- Policy level: **Strong recommendation (against)**
- Differences of opinion: None

Supporting Text

In summary, antiviral therapy alone (acyclovir or valacyclovir) is not recommended in the treatment of Bell's palsy due to lack of effectiveness of currently available drugs, unnecessary cost, and the potential for drug-related complications. Although this may well be a class effect for this group of drugs, it is theoretically possible that other antivirals presently available or developed in the future may be shown to be effective.

hours of symptom onset for patients with Bell's palsy.

Option based on randomized controlled trials with minor limitations and observational studies with equilibrium of benefit and harm.

Action Statement Profile

- Aggregate evidence quality: **Grade B**
- Level of confidence in evidence: Medium, because the studies cannot exclude a small effect
- Benefit: Small potential improvement in facial nerve function
- Risks, harms, costs: Treatment side effects, cost of treatment
- Benefit-harm assessment: Equilibrium of benefit and harm
- Value judgments: Although the data were weak, the risks of combination therapy were small
- Intentional vagueness: None
- Role of patient preferences: Large; significant role for shared decision making
- Exceptions: Diabetes, morbid obesity, and previous steroid intolerance. Pregnant women should be treated on an individualized basis
- Policy level: **Option**
- Differences of opinion: None

Supporting Text

In summary, antiviral therapy in addition to steroid therapy has not been proven to be of benefit in the treatment of Bell's palsy in large, high-quality clinical trials, although a small benefit cannot be completely excluded. Due to the potential of a small benefit in facial nerve functional recovery and the relatively low risk of antiviral therapy, the GDG concluded that patients may be offered combination therapy if treated within 72 hours of onset of Bell's palsy, with a large role for shared decision making.

NGC Note: Refer to the original guideline document for the complete text supporting the above recommendations. Refer to either the NGC summary or the original guideline document for additional

Strength of Evidence and Recommendation Grading Schemes

AAN (2012)	**Classification of Evidence** **Class I**: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a. Concealed allocation b. Primary outcome(s) clearly defined c. Exclusion/inclusion criteria clearly defined d. Adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. **Class II**: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-e above OR a randomized controlled trial (RCT) in a representative population that lacks one criteria a-d. **Class III**: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement*. **Class IV**: Evidence from uncontrolled studies, case series, case reports, or expert opinion. *Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data). **Strength of Recommendations**

population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

AAO-HNSF (2013)

Evidence Levels for Grades of Evidence*

Grade	Treatment and Harm	Diagnosis
A	Well-designed randomized controlled trials performed on a population similar to the guideline's target population	Systematic review of cross-sectional studies with consistently applied reference standard and blinding
B	Randomized controlled trials; overwhelmingly consistent evidence from observational studies	Individual cross-sectional studies with consistently applied reference standard and blinding

	(case control and cohort design)	studies, case-control studies, or studies with poor, nonindependent, or inconsistently applied reference standards
D	Mechanism-based reasoning or case reports	
X	Exceptional situations where validating studies cannot be performed and there is a clear preponderance of benefit over harm	

*American Academy of Pediatrics (AAP) classification scheme updated for consistency with current level of evidence definitions.

Guideline Definitions for Evidence-based Statements

Statement	Definition	Implication

Recommendation	recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B).* In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

	means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C).* In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option	An option means that either the quality of evidence that exists is suspect (Grade D)* or that well-done studies (Grade A, B, or C)* show little clear advantage to one approach vs another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.

	means there is both a lack of pertinent evidence (Grade D)* and an unclear balance between benefits and harms.	little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit vs harm; patient preference should have a substantial influencing role.

*See above for definitions of evidence grades.

Methodology

Click on the links below for details of guideline development methodology

AAN (2012)	AAO-HNSF (2013)

AAN and AAO-HNSF performed searches of electronic databases to collect the evidence base for their guidelines; both developers provide relevant details of the process including the names of databases searched, date ranges applied, and specific keywords used. To assess the quality and strength of the selected evidence, the two guideline developers weighted it according to a rating scheme. AAO-HNSF also used expert consensus.

Methods used to analyze the evidence were similar between the two groups, with both having performed a systematic review (with evidence tables) of the evidence. AAO-HNSF also reviewed published meta-analyses. With regard to the formulation of recommendation statements, AAN and AAO-HNSF employed expert consensus, and both rate the strength of the recommendations according to a scheme. To validate their guidelines, both developers sought internal and external peer review.

Benefits

AAN (2012)	Appropriate treatment and management of patients with Bell palsy
AAO-HNSF (2013)	By focusing on opportunities for quality improvement, the guideline should improve diagnostic accuracy, facilitate prompt intervention, decrease inappropriate variations in management, reduce unnecessary tests and imaging procedures, and improve paralysis and rehabilitative outcomes for affected patients. For benefits of specific interventions considered in the guideline, see the "Major Recommendations" field of the NGC summary.

Harms

AAN (2012)	**Side Effects of Steroids and Antiviral Agents** • All studies reported adverse events (AEs) from steroids. In general, these were minor and temporary. The most common AEs reported were insomnia and dyspepsia. • None of the studies demonstrated a significant increase in any AE for patients randomized to an antiviral agent.
AAO-HNSF (2013)	**Oral Corticosteroids** Treatment of Bell's palsy with oral corticosteroids is not without risk. Known side effects of oral corticosteroid use include gastrointestinal disturbances, reactivation of peptic ulcer disease, loss of control of glucose levels, elevated blood pressure, peripheral edema, and mood swings or episodes of acute psychosis. Although rare, avascular necrosis of the femoral head has been reported. Pregnant patients and patients with diabetes were routinely excluded from randomized trials. Accordingly, these patients should be handled on an individualized basis.

	gastrointestinal related and include nausea, vomiting, and diarrhea, with rare severe reactions, including hives, bronchospasm, angioedema, and hepatic or renal failure. Adverse events from antiviral therapy were rarely reported in clinical trials of patients with Bell's palsy and were limited to gastrointestinal upset. Accordingly, no serious adverse events from antiviral therapy were noted in the Bell's palsy literature. • Antiviral therapy may also carry an increased risk for pregnant patients.

Contraindications

AAN (2012)	Groups potentially requiring further consideration before the use of steroids include patients with brittle diabetes mellitus, morbid obesity, osteopenia and those with prior history of steroid intolerance.
AAO-HNSF (2013)	Not stated

Abbreviations

AAN, American Academy of Neurology

AAO-HNSF, American Academy of Otolaryngology-Head and Neck Surgery Foundation

GDG, Guideline Development Group

Status

This synthesis was prepared by ECRI Institute on August 14, 2014. The information was verified by AAO-HNSF on September 3, 2014 and by AAN on September 19, 2014.