AAN Pocket Guidelines
Summaries of AAN Evidence-based Guidelines

This pocket guide is an educational resource of the American Academy of Neurology (AAN). It is designed to provide members with evidence-based guideline recommendations to assist in decision making in patient care. AAN evidence-based guidelines are based on assessments of current scientific and clinical information and are not intended to exclude reasonable alternative methodologies. The AAN recognizes that patient care decisions are the prerogative of the patient and the physician and are based on the circumstances involved. Neurologists are encouraged to review carefully each AAN evidence-based guideline at www.aan.com to understand all of the presented recommendations.

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American Academy of Neurology Evidence-based Guidelines

See www.aan.com for more information.
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How AAN Guidelines Are Created

AAN evidence-based guidelines consist of a formalized review of the literature that serves as the foundation for evidence-based practice recommendations. The literature review of a guideline is distinct from a typical literature review in that it is systematic and transparent. The recommendations of the guideline are also distinct in that they are fundamentally evidence based.

Authors identify a clinical question for which AAN members could benefit from evidence-based guidance. Then they answer the question by employing a methodology most likely to lead to the correct answer. Asking and answering the question form the backbone of both the guideline development process and the resulting manuscript. Both clearly follow this progression:

ASK A CLINICAL QUESTION
↓
FIND AND ANALYZE RELEVANT EVIDENCE
↓
STATE CONCLUSIONS
↓
MAKE RECOMMENDATIONS

Classification of Evidence Rating Key

Strength of Recommendations*

(A) = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for a given condition (or test, predictor) in the specified population.

(B) = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition (or test, predictor) in the specified population.

(C) = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition (or test, predictor) in the specified population.

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

The classification of evidence system used by the AAN has evolved over time. Please refer to the specific guideline for information on how articles were classified and translated into recommendations.

*Technology assessment ratings are shown in parentheses.
Clinical Context
Clinical context is provided for some AAN evidence-based guidelines in order to place them in perspective with current practice habits and challenges. No formal practice recommendations should be inferred. For some guidelines presented here, the clinical context is abridged; to read it in its entirety, see the published guidelines.

AAN Guideline Updating and Reaffirmation Process
According to the Agency for Healthcare Research and Quality, guidelines have a 10% chance of being out-of-date 3 years after publication. Therefore, the AAN has adopted a two-tiered system for evaluating guidelines to ensure that out-of-date guidelines are identified and updated in a timely manner:

- **Annual request of authors to evaluate currency**

  **Triennial updating literature search and evaluation of methodology**

If new evidence is available that will significantly change the guideline, a complete update or an addendum is initiated on the basis of the number of changes required.

If a guideline is out-of-date and the topic is not a priority for reevaluation, the guideline is retired.

If the guideline recommendations are still current, the guideline is reaffirmed.
Guidelines

The following pages are a summary of two AAN guidelines on amyotrophic lateral sclerosis (ALS):


Tools & Resources

Please refer to www.aan.com to access the full 2009 guideline updates and the following companion tools:

• Clinician Summaries
• Patient Summaries
• Slide Presentation
• Clinical Example
• Posters
• Podcast

Update: Care in ALS: Drug, Nutritional, and Respiratory Therapies (2009)

Endorsed by the American Association of Neuromuscular and Electrodiagnostic Medicine.

Important treatments are available for patients with amyotrophic lateral sclerosis (ALS) that are underutilized. Noninvasive ventilation (NIV), percutaneous endoscopic gastrostomy (PEG), and riluzole are particularly important and have the best evidence. More studies are needed to examine the best tests of respiratory function in ALS, as well as the optimal time for starting PEG, the impact of PEG on quality of life (QOL) and survival, and the effect of vitamins and supplements on ALS.

Recommendations

Drug Therapies

• Riluzole should be offered to slow disease progression in patients with ALS (A*).

• There are insufficient data at this time to support or refute treatment with lithium carbonate in patients with ALS (U).

Nutritional Therapies

• In patients with ALS with impaired oral food intake, enteral nutrition via PEG should be considered to stabilize body weight (B).

• PEG should be considered for prolonging survival in patients with ALS (B).

• There are insufficient data to support or refute specific timing of PEG insertion in patients with ALS (U).
• There are insufficient data to support or refute PEG for improving QOL in patients with ALS (U).

• Creatine, in doses of 5 g to 10 g daily, should not be given as treatment for ALS because it is not effective in slowing disease progression (A).

• High-dose vitamin E should not be considered as treatment for ALS (B).

• The equivocal evidence regarding low-dose vitamin E permits no recommendation (U).

Respiratory Therapies

• NIV should be considered to treat respiratory insufficiency in ALS, both to lengthen survival and to slow the rate of FVC decline (B).

• NIV may be considered to enhance QOL in patients with ALS who have respiratory insufficiency (C).

• NIV may be considered at the earliest sign of nocturnal hypoventilation or respiratory insufficiency in order to improve compliance with NIV in patients with ALS (C).

• Nocturnal oximetry may be considered to detect hypoventilation (regardless of the forced vital capacity [FVC]) (C).

• Supine FVC and maximal inspiratory pressure (MIP) may be considered useful in routine respiratory monitoring, in addition to the erect FVC (C).

• Sniff nasal pressure (SNP) may be considered to detect hypercapnia and nocturnal hypoxemia (C).

• Tracheostomy invasive ventilation (TIV) may be considered to preserve QOL in patients with ALS who want long-term ventilatory support (C).

• Mechanical insufflation/exsufflation (MIE) may be considered to clear secretions in patients with ALS who have reduced peak cough flow, particularly during an acute chest infection (C).

• There are insufficient data to support or refute high-frequency chest wall oscillation (HFCWO) for clearing airway secretions in patients with ALS (U).

• Clinical Context: Medications with mucolytics, a B-receptor antagonist, nebulized saline, or an anticholinergic bronchodilator are widely used; however, no controlled studies exist in ALS.

Clinical Context

• The ALS patient CARE database was developed with the hope of standardizing new and effective therapies for patients with ALS and tracking outcomes to raise the standard of care. Data obtained from the ALS CARE program have shown that the underutilization of many therapies has persisted in the years since the previous guideline, though there have been gains. These findings suggest that an evidence-based guideline may over time become more widely accepted and change practice. However, the persistent underutilization of therapies that improve survival and QOL poses a challenge for ALS clinicians to continue to raise the standard of care for patients with ALS.
• Figures 1 and 2 present approaches to nutritional and respiratory management in patients with ALS.

**Figure 1. Nutrition management algorithm**

*Diagnosis: ALS*

- Clinic visits every 3 months
- Early dysphagia detected
- *Nutritional education including PEG*[^2]

Monitor **body weight**

- *Dysphagia assessment instrument*[^1]

Monitor **respiratory status** (FVC, MIP, etc.)

- Monitor body weight
- Clinic visits every 3 months
- Symptom progression[^3] or continuing weight loss

**Discuss PEG to stabilize weight and possibly prolong survival**

- FVC > 50%
  - Low risk for PEG
  - PEG accepted
  - Oral intake as tolerated

- FVC 30-50%
  - Moderate risk
  - Enteral nutrition via PEG as needed

- FVC < 30%
  - High risk
  - PEG declined
  - Oral intake as tolerated
  - Palliative IV hydration
  - Palliative NG feeding

[^1]: *e.g., bulbar questions in the Amyotrophic Lateral Sclerosis Functional Rating Scale, or other instrument.*[^2]: *Percutaneous endoscopic gastrostomy: rule out contraindications.*[^3]: *Prolonged meal time; ending meal prematurely because of fatigue; accelerated weight loss due to poor caloric intake; family concern about feeding difficulties. Text in bold = evidence-based. Text in italics = consensus-based.*
Symptom evaluation¹ and PFTs; initiate NIV orientation, Pneumovax and flu vaccine

Orthopnea or SNP < 40cm or MIP < -60cm or Abnl nocturnal oximetry or FVC < 50%

Consider NIV

NIV tolerated?

No

Further education regarding documented benefits; evaluate reasons for noncompliance

Reintroduce NIV

Not successful²

Hospice referral for palliative care

Invasive ventilation

Yes

Ongoing evaluations and adjustment of pressures

Successful

Unable to maintain pO₂ > 90%, pCO₂ < 50mmHg or unable to manage secretions

Suction machine

Manual assisted cough

Mechanical inexsufflator

Treat sialorrhea/phlegm

PCEF < 270 L/min

Diagnosis: ALS

¹Symptoms suggestive of nocturnal hypoventilation: Frequent arousals, morning headaches, excessive daytime sleepiness, vivid dreams. ²If NIV is not tolerated or accepted in the setting of advancing respiratory compromise, consider invasive ventilation or referral to hospice.

PFT = pulmonary function tests, PCEF = peak cough expiratory flow, NIV = noninvasive ventilation, SNP = sniff nasal pressure, MIP = maximal inspiratory pressure, FVC = forced vital capacity (supine or erect), Abnl.nocturnal oximetry = pO₂ < 4% from baseline. Text in bold = evidence-based. Text in italics = consensus-based.

* Evidence rating key can be found on page 5 of this pocket guide.

**Update: Care in ALS: Multidisciplinary Care, Symptom Management, and Cognitive/Behavioral Impairment (2009)**

Endorsed by the American Association of Neuromuscular and Electrodiagnostic Medicine.

Many important areas of amyotrophic lateral sclerosis (ALS) have been little studied. More high-quality, controlled studies of symptomatic therapies and palliative care are needed to guide management and assess outcomes in patients with ALS.
Recommendations

Breaking the News

• There is insufficient evidence to support or refute any specific method of disclosing the diagnosis in ALS (U*).

• Clinical Context: Useful strategies have been developed for disclosing a diagnosis of cancer (see appendix e-1 of the published guideline).

Multidisciplinary Care

• Specialized multidisciplinary clinic referral should be considered for patients with ALS to optimize health care delivery (B) and prolong survival (B).

• Clinical Context: Specialized multidisciplinary clinic referral may be considered to enhance quality of life (QOL) (C).

Symptomatic Management

• In patients with ALS who have medically refractory sialorrhea, botulinum toxin type B (BoNT-B) should be considered (B).

• In patients with ALS who have medically refractory sialorrhea, low-dose radiation therapy to the salivary glands may be considered (C).

• Clinical Context: In ALS and other diseases, anticholinergic medications are generally tried first to reduce sialorrhea, although effectiveness is unproven. Botulinum toxin (BoNT) has been effective in controlled trials in parkinsonism as well as ALS.

• If approved by the US Food and Drug Administration (FDA), and if side effects are acceptable, dextromethorphan/quinidine (DM)/(Q) should be considered for symptoms of pseudobulbar affect in patients with ALS (B). (Since publication of this guideline, the FDA has approved DM/Q for this indication.)

• In patients developing fatigue while taking riluzole, once risks of fatigue vs modest survival benefits have been discussed, withdrawing the drug may be considered (C).

• There are insufficient data to support or refute any specific intervention for the treatment of cramps in ALS (U).

• There are insufficient data to support or refute exercise or medication for treating spasticity in ALS (U).

• Clinical Context: In multiple sclerosis and cerebral palsy, benzodiazepam, baclofen, dantrolene, and tizanidine are effective in reducing spasticity-related symptoms.

• There are insufficient data to support or refute specific treatments for depression, anxiety, or insomnia in ALS (U).

• Clinical Context: There is consensus among experts that depression should be treated in patients with ALS; however, there are no controlled studies of benefit or harm.
Cognitive and Behavioral Impairment

- Screening for cognitive and behavioral impairment should be considered in patients with ALS (B).
- Screening tests of executive function may be considered to detect cognitive impairment in patients with ALS prior to confirmation with formal neuropsychological evaluation (C).
- There are insufficient data to support or refute the impact of cognitive and behavioral impairment on management in ALS (U).
- There are insufficient data to support or refute treatment of cognitive or behavioral impairment in ALS (U).

Communication

- There are insufficient data to support or refute treatment to optimize communication in ALS (U).

Palliative Care

- There are insufficient data to support or refute specific treatments for pain and dyspnea in late-stage ALS (U).
- There are insufficient data to support or refute hospice, spiritual care, or advance directives in ALS (U).
- There are insufficient data to support or refute specific strategies for withdrawal of ventilation in ALS (U).
- Clinical Context: Protocols based on consensus for withdrawal of mechanical ventilation in intensive care units (Class IV) include counseling and symptom control with opioids, benzodiazepines, and anticholinergic medications. The authors could find no controlled studies in any disease.

* Evidence rating key can be found on page 5 of this pocket guide.
Guideline

Tools & Resources
Please refer to www.aan.com to access the full guideline and the following companion tools:
- Clinician Summary
- Parent/Caregiver Summary
- Slide Presentation

Summary
Autism, autistic spectrum disorder, and pervasive developmental disorder encompass a wide continuum of associated cognitive and neurobehavioral disorders. The core defining features are impaired socialization, impaired verbal and nonverbal communication, and restricted and repetitive patterns of behavior. This guideline reviews the available empirical evidence and gives specific recommendations for the identification of children with autism.


Recommendations
Routine Developmental Surveillance
- Developmental surveillance should be performed at all well-child visits from infancy through school age, and at any age thereafter if concerns are raised about social acceptance, learning, or behavior (B*).
- Recommended developmental screening tools include the Ages and Stages Questionnaire, the BRIGANCE® Screens, the Child Development Inventories, and the Parents’ Evaluations of Developmental Status (B).
- Because of the lack of sensitivity and specificity, the Denver-II (DDST-II) and the Revised Denver Pre-Screening Developmental Questionnaire (R-DPDQ) are not recommended for primary-care developmental surveillance (B).
- Further developmental evaluation is required whenever a child fails to meet any of the following milestones: babbling by 12 months; gesturing (e.g., pointing, waving bye-bye) by 12 months; single words by 16 months; two-word spontaneous (not just echolalic) phrases by 24 months; loss of any language or social skills at any age (B).
- Siblings of children with autism should be carefully monitored for acquisition of social, communication, and play skills, and the occurrence of maladaptive behaviors. Screening should be performed not only for autism-related symptoms but also for language delays, learning difficulties, social problems, and anxiety or depressive symptoms (B).
• Screening specifically for autism should be performed on all children failing routine developmental surveillance procedures using one of the validated instruments—the CHecklist for Autism in Toddlers (CHAT) or the Autism Screening Questionnaire (B).

• Laboratory investigations recommended for any child with developmental delay and/or autism include audiologic assessment and lead screening (B). Early referral for a formal audiologic assessment should include behavioral audiometric measures, assessment of middle-ear function, and electrophysiologic procedures, using experienced pediatric audiologists with current audiologic testing methods and technologies (B).

• Lead screening should be performed in any child with developmental delay and pica. Additional periodic screening should be considered if the pica persists (B).

**Diagnosis and Evaluation of Autism**

• Genetic testing in children with autism, specifically high-resolution chromosome studies (karyotype) and DNA analysis for Fragile X (FraX), should be performed in the presence of mental retardation (or if mental retardation cannot be excluded), if there is a family history of FraX or undiagnosed mental retardation, or if dysmorphic features are present (A). However, there is little likelihood of positive karyotype or FraX testing in the presence of high-functioning autism.

• Selective metabolic testing should be initiated by the presence of suggestive clinical and physical findings such as the following: if lethargy, cyclic vomiting, or early seizures are evident; the presence of dysmorphic or coarse features; evidence of mental retardation or if mental retardation cannot be ruled out; or if occurrence or adequacy of newborn screening for a birth is questionable (A).

• There is inadequate evidence at the present time to recommend an EEG study in all individuals with autism. Indications for an adequate sleep-deprived EEG with appropriate sampling of slow-wave sleep include clinical seizures or suspicion of subclinical seizures, and a history of regression (clinically significant loss of social and communicative function) at any age, but especially in toddlers and preschoolers (B).

• Recording of event-related potentials and magnetoencephalography are research tools at the present time, without evidence of routine clinical utility (B).

• There is no clinical evidence to support the role of routine clinical neuroimaging in the diagnostic evaluation of autism, even in the presence of megalencephaly (B).
• There is inadequate supporting evidence for hair analysis, celiac antibodies, allergy testing (particularly food allergies for gluten, casein, candida, and other molds), immunologic or neurochemical abnormalities, micronutrients such as vitamin levels, intestinal permeability studies, stool analysis, urinary peptides, mitochondrial disorders (including lactate and pyruvate), thyroid function tests, or erythrocyte glutathione peroxidase studies (B).

• Figure 3 presents an algorithm for routine surveillance and for diagnosis and evaluation.

Figure 3. Practice Parameter Algorithm

Level One: Routine Development Surveillance
By all providers at every well-child visit (e.g., PEDS, ASQ, CDIs, or BRIGANCE®)

Absolute Indications for Immediate Evaluation:
No babbling, or pointing or other gesture by 12 months
No single words by 16 months
No 2-word spontaneous (not echolalic) phrases by 24 months
ANY loss of ANY language or social skill at ANY age

Laboratory investigation:
Formal audiological assessment, lead screen if pica present

Specifically screen for autism:
CHAT, Autism Screening Questionnaire (Australian Scale for Asperger’s Syndrome, PDDST-II-Stage 1)

Refer to early intervention or local school district
Proceed to Level Two

Rescreen at next visit

Pass

Fail

Level Two: Diagnosis and Evaluation of Autism
Formal diagnostic procedures by experienced clinician
History and neurological evaluation
Specific evaluations to determine developmental profile
Expanded laboratory evaluation only if indicated

* Evidence rating key can be found on page 5 of this pocket guide.
Guideline
This is a summary of the AAN guideline on therapies for benign paroxysmal positional vertigo (BPPV) (*Neurology* 2008;70:2067–2074).

Tools & Resources
Please refer to [www.aan.com](http://www.aan.com) to access the full guideline and the following companion tools:

- Clinician Summary
- Patient/Caregiver Summary
- Slide Presentation
- Clinical Example
- Poster
- Video
- Podcast

Summary
Repositioning maneuvers are believed to treat BPPV by moving the canaliths from the semicircular canal to the vestibule from which they are absorbed. There are a number of repositioning maneuvers in use, but they lack standardization. The canalith repositioning procedure (CRP) has strong evidence supporting its use, whereas there is only weak evidence supporting the Semont maneuver. The figures and web-based video clips do not include all variations but represent those maneuvers and treatments used in the Class I and Class II studies that are reviewed as well as several others in common use.

Therapies for Benign Paroxysmal Positional Vertigo (2008)

**Recommendations**

- Strong evidence supports CRP (see figure 4), which is established as an effective and safe therapy that should be offered to patients of all ages with posterior semicircular canal BPPV (A*).
- There is insufficient evidence to prove the benefit of postmaneuver restrictions in patients treated with CRP (U).
- Mastoid oscillation is probably of no added benefit to patients treated with CRP for posterior canal BPPV (C).
- Self-administered Brandt-Daroff exercises or habituation exercises are less effective than CRP (C).
- Weak evidence indicates that the Semont maneuver is possibly effective for BPPV (see figure 5) (C).
- Insufficient evidence exists to compare the relative effectiveness of the Semont maneuver versus CRP (U).
• There is insufficient evidence to show that CRP or Semont maneuvers when performed by the patient are as effective as when performed by an experienced clinician (U).

• No recommendation can be made for treating horizontal canal BPPV (see figure 6) (U).

• No recommendation can be made for treating anterior canal BPPV (see figure 6) (U).

• There is no evidence to support or refute a recommendation on medication use for routine treatment for BPPV (U).

• There is insufficient evidence based on randomized controlled trials to prove or disprove the effectiveness of posterior semicircular canal occlusion or singular neurectomy as treatment for BPPV (U).

**Figure 4. Canalith repositioning procedure. A stepwise method of performing the canalith repositioning procedure for Right BPPV**

*Step 1* – Seat the patient on a table positioned so he or she may be taken back to the head-hanging position with the neck in slight extension. Stabilize the head with your hands and move the head 45 degrees toward the side you will test. Move the head, neck, and shoulders en bloc to the head-hanging position (Step 2).
**Step 2** – Observe the eyes, holding them open if necessary. Wait for all the nystagmus to stop and then give it about half as long as it lasted (usually about 10 seconds after it stops).

**Step 3** – Keeping the head back with the neck slightly hyperextended, turn the head about 90 degrees toward the opposite side and wait 20 to 30 seconds. Hold the patient’s head to avoid neck strain.

**Step 4** – Roll the patient all the way on to his or her side and then turn the head to face the ground and hold it there 10 to 15 seconds. There should be no nystagmus. If the patient reports a little dizziness, it is usually a favorable sign that the particles are moving and the treatment will be successful.

**Step 5** – Keeping the head somewhat in the same position toward the shoulder, have the patient sit up. Hold on to him or her for a moment because some patients feel a sudden but very brief tilt when sitting up.

**REPEAT:** After waiting 30 seconds or so, repeat the whole maneuver. If there is no paroxysmal nystagmus or symptom during Dix Hallpike positioning (Steps 1 and 2) when repeated, CRP has likely been successful.

**Figure 5. Semont maneuver. Steps in performing Semont’s liberatory maneuver (for right-sided BPPV)**

**Step 1** – Start with the patient sitting on a table with head turned away from the affected side.

**Step 2** – Quickly put the patient into the side-lying position, toward the affected side with the head turned up 45 degrees. Nystagmus will develop in this position, but hold it for 10 to 20 seconds after nystagmus subsides.

**Step 3** – Quickly move the patient in a swooping motion all the way to the opposite side, keeping the head at the same angle relative to the shoulders. Keep the patient in this position for about 30 to 60 seconds and then have the patient sit up at a casual pace.
Figure 6. Membranous labyrinth depicting the orientation of the semicircular canals (ducts)

* Evidence rating key can be found on page 5 of this pocket guide.
Guidelines

The following pages summarize two AAN guidelines on severe brain injury and brain death:

Prediction of Outcome in Comatose Patients after CPR (Neurology 2006;67:203–210; reaffirmed October 2009)

Update: Determining Brain Death in Adults (Neurology 2010;74:1911–1918)

Tools & Resources

Please refer to www.aan.com to access the full coma guideline, the full brain death guideline update, and the following companion tools:

• Clinician Summaries  • Slide Presentation  • Background/Data
• Family/Caregiver Summaries  • Clinical Example

Prediction of Outcome in Comatose Patients after CPR (2006; reaffirmed 2009)

This is a summary of the AAN guideline reviewing all available evidence on the prognostic value of the clinical examination and ancillary investigations (electrophysiologic, biochemical, and radiologic) for poor outcome in comatose survivors after cardiopulmonary resuscitation (CPR). Poor outcome is defined as death, unconsciousness after 1 month, or unconsciousness or severe disability after 6 months.

Recommendations

Clinical Examination

• Prognosis cannot be based on the circumstances of CPR (B*).
• Prognosis cannot be based on elevated body temperature alone (C).
• The prognosis is invariably poor in comatose patients with absent pupillary or corneal reflexes, or absent or extensor motor responses 3 days after cardiac arrest (A).
• Patients with myoclonus or status epilepticus within the first day following a primary circulatory arrest have a poor prognosis (B).

Electrophysiological Tests

• Burst suppression or generalized epileptiform discharges on EEG predicted poor outcomes but with insufficient prognostic accuracy (C).
• The assessment of poor prognosis can be guided by the presence of bilaterally absent cortical somatosensory evoked potentials (SSEPs) (N20 response) within 1 to 3 days (B).
Biochemical Markers

• Serum neuron-specific enolase (NSE) levels > 33 µg/L at day 1 to day 3 post-CPR accurately predict poor outcome (B). There are inadequate data to support or refute the prognostic value of other serum and cerebrospinal fluid (CSF) biochemical markers in comatose patients following CPR (U).

• There are inadequate data to support or refute the prognostic value of intracranial pressure (ICP) monitoring (U).

Neuroimaging Studies

• There are inadequate data to support or refute whether neuroimaging is indicative of poor outcome (U).

Confounding Factors

• Some factors may confound the reliability of the clinical exam and ancillary tests. Major confounders could include the use or prior use of sedatives or neuromuscular blocking agents, induced hypothermia therapy, presence of organ failure (e.g., acute renal or liver failure), or shock (e.g., cardiogenic shock requiring inotropes). However, studies in comatose patients have not systematically addressed the role of these confounders in neurologic assessment.

Communication with Family and Further Decision Making

• The complexity of evaluation and prognostication require neurologic professional expertise. Figure 7 summarizes the usefulness of the most important prognostic variables in comatose patients after cardiac arrest. More than one scheduled meeting with the family is generally required to facilitate a trusting relationship. The neurologist can explain that the prognosis is largely based on clinical examination with some help from laboratory tests. In a conversation with the family, the neurologist may further articulate that the chance of error is very small. When a poor outcome is anticipated, the need for continuation of life-sustaining measures (mechanical ventilation, use of vasopressors or inotropic agents to hemodynamically stabilize the patient) must be discussed. When fully informed and more certain, the family or proxy is allowed to rethink resuscitation orders or even to adjust the level of care to comfort measures only. However, these decisions should be made after best interpretation of advance directives or the previously voiced wishes of the patient.
### Decision Algorithm for Use in Prognostication of Comatose Survivors after CPR

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>1. Exclude major confounders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. No brainstem reflexes at any time (pupil, cornea, oculocephalic, cough)</td>
<td>Yes</td>
<td>Brain death testing</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Indeterminate outcome</td>
</tr>
<tr>
<td>3. Day 1: Myoclonus status epilepticus</td>
<td>Yes</td>
<td>Poor outcome FPR 0% (0-8.8)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Indeterminate outcome</td>
</tr>
<tr>
<td>4. Day 1-3: Serum NSE $&gt;33$ ug/L</td>
<td>Yes</td>
<td>Poor outcome FPR 0% (0-3)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Indeterminate outcome</td>
</tr>
<tr>
<td>5. Day 3: Absent pupil or corneal reflexes; extensor or absent motor response</td>
<td>Yes</td>
<td>Poor outcome FPR 0% (0-3)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Indeterminate outcome</td>
</tr>
<tr>
<td>6. Day 1-3: SSEP absent N20 responses</td>
<td>Yes</td>
<td>Poor outcome FPR 0.7% (0-3.7)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Indeterminate outcome</td>
</tr>
</tbody>
</table>

Decision algorithm for use in prognostication of comatose survivors after CPR. The numbers in parentheses are exact 95% confidence intervals. The confounding factors potentially could diminish prognostic accuracy of this algorithm. †NSE = neuron-specific enolase; SSEP = somatosensory evoked potential; FPR = false positive rate. ††These tests may not be available on a timely basis. Serum NSE testing may not be sufficiently standardized.

* Evidence rating key can be found on page 5 of this pocket guide.

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**Update: Determining Brain Death in Adults** *(2010)*

Endorsed by the American College of Radiology, the Association of Organ Procurement Organizations, the Child Neurology Society, the Neurocritical Care Society, the Radiological Society of North America, and the Society of Critical Care Medicine.

### Definition of Brain Death

This is a summary of the AAN guideline on determining brain death in adults. The Uniform Determination of Death Act (UDDA) defines brain death as the “1) irreversible cessation of circulatory and respiratory functions or 2) irreversible cessation of all functions of the entire brain, including the brainstem” and states that “a determination of death must be made with accepted medical standards.” The UDDA does not define “accepted medical standards.” The AAN’s 1995 guideline emphasized the three clinical findings...
necessary to confirm irreversible cessation of all functions of the entire brain, including the brainstem: coma (with a known cause), absence of brainstem reflexes, and apnea. Despite the 1995 publication, considerable practice variation remains.

**Recommendations**

- The criteria for the determination of brain death given in the 1995 AAN guideline have not been invalidated by published reports of neurologic recovery in patients who fulfill these criteria (U*).

- There is insufficient evidence to determine the minimally acceptable observation period to ensure that neurologic functions have ceased irreversibly (U).

- Complex-spontaneous motor movements and false-positive triggering of the ventilator may occur in patients who are brain dead (C).

- There is insufficient evidence to determine the comparative safety of techniques used for apnea testing (U).

- There is insufficient evidence to determine if newer ancillary tests accurately confirm the cessation of function of the entire brain (U).

**Clinical Context**

- This review highlights severe limitations in the current evidence base. Indeed, there is only one study that prospectively derived criteria for the determination of brain death.

- Despite the paucity of evidence, much of the framework necessary for the development of “accepted medical standards” for the declaration of brain death is based on straightforward principles. These principles can be derived from the definition of brain death provided by the UDDA. To determine “cessation of all functions of the entire brain, including the brainstem,” physicians must determine the presence of unresponsive coma, the absence of brainstem reflexes, and the absence of respiratory drive after a CO$_2$ challenge. To ensure that the cessation of brain function is “irreversible,” physicians must determine the cause of coma, exclude mimicking medical conditions, and observe the patient for a period of time to exclude the possibility of recovery.

- The UDDA-derived principles define the essential elements needed to determine brain death. However, because of the deficiencies in the evidence base, clinicians must exercise considerable judgment when applying the criteria in specific circumstances.

- A checklist is provided (see figure 8) to aid in documenting the application of criteria.
Figure 8. Checklist for determination of brain death

Prerequisites (all must be checked)
- Coma, irreversible and cause known.
- Neuroimaging explains coma.
- CNS depressant drug effect absent (if indicated toxicology screen; if barbiturates given, serum level <10 µg/mL).
- No evidence of residual paralytics (electrical stimulation if paralytics used).
- Absence of severe acid-base, electrolyte, endocrine abnormality.
- Normothermia or mild hypothermia (core temperature >36°C).
- Systolic blood pressure ≥100 mm Hg.
- No spontaneous respirations.

Examination (all must be checked)
- Pupils nonreactive to bright light.
- Corneal reflex absent.
- Oculocephalic reflex absent (tested only if C-spine integrity ensured).
- Oculovestibular reflex absent.
- No facial movement to noxious stimuli at supraorbital nerve, temporomandibular joint.
- Gag reflex absent.
- Cough reflex absent to tracheal suctioning.
- Absence of motor response to noxious stimuli in all four limbs (spinally mediated reflexes are permissible).

Apnea testing (all must be checked)
- Patient is hemodynamically stable.
- Ventilator adjusted to provide normocarbia (PaCO₂ 35–45 mm Hg).
- Patient preoxygenated with 100% FiO₂ for >10 minutes to PaO₂ >200 mm Hg.
- Patient well-oxygenated with a PEEP of 5 cm of water.
- Provide oxygen via a suction catheter to the level of the carina at 6 L/min or attach T-piece with CPAP at 10 cm H₂O.
- Disconnect ventilator.
- Spontaneous respirations absent.
- Arterial blood gas drawn at 8–10 minutes, patient reconnected to ventilator.
- PCO₂ ≥60 mm Hg, or 20 mm Hg rise from normal baseline value.

OR:
- Apnea test aborted.

Ancillary testing (only one needs to be performed) (to be ordered only if clinical examination cannot be fully performed due to patient factors, or if apnea testing inconclusive or aborted)
- Cerebral angiogram
- HMPAO SPECT
- EEG
- TCD

Time of death (DD/MM/YY) _______/ _______ / _______

Name of physician and signature  _____________________________________________
Practical (Non-Evidence-based) Guidance for Determination of Brain Death

• Many of the details of the clinical neurologic examination to determine brain death cannot be established by evidence-based methods. The detailed brain death evaluation protocol that follows is intended as a useful tool for clinicians. It must be emphasized that this guidance is opinion-based. Alternative protocols may be equally informative. The determination of brain death can be considered to consist of four steps.

The Clinical Evaluation (Prerequisites)

Establish Irreversible and Proximate Cause of Coma

• The cause of coma can usually be established by history, examination, neuroimaging, and laboratory tests.

• Exclude the presence of a CNS-depressant drug effect by history, drug screen, calculation of clearance using five times the drug’s half-life (assuming normal hepatic and renal function), or, if available, drug plasma levels below the therapeutic range. Prior use of hypothermia (e.g., after cardiopulmonary resuscitation) for cardiac arrest may delay drug metabolism. The legal alcohol limit for driving (blood alcohol content 0.08%) is a practical threshold below which an examination to determine brain death could reasonably proceed.

• There should be no recent administration or continued presence of neuromuscular blocking agents (this can be defined by the presence of a train of four twitches with maximal ulnar nerve stimulation).

• There should be no severe electrolyte, acid-base, or endocrine disturbance (defined by severe acidosis or laboratory values markedly deviated from the norm).

Achieve Normal Core Temperature

• In most patients, a warming blanket is needed to raise the body temperature and maintain a normal or near-normal temperature (>36°C). After the initial equilibration of arterial carbon dioxide (CO₂) with mixed central venous CO₂, the partial pressure of CO₂ (PaCO₂) rises steeply, but then more slowly when the body metabolism raises PaCO₂. To avoid delaying an increase in PaCO₂, normal or near-normal core temperature is preferred during the apnea test.

Achieve Normal Systolic Blood Pressure

• Hypotension from loss of peripheral vascular tone or hypovolemia (often related to diabetes insipidus) is common; vasopressors or vasopressin are often required. Neurologic examination is usually reliable with a systolic blood pressure ≥100 mm Hg.

Perform One Neurologic Examination (Sufficient to Pronounce Brain Death in Most US States)

• If a certain period of time has passed since the onset of the brain insult to exclude the possibility of recovery (in practice, usually several hours),
one neurologic examination should be sufficient to pronounce brain death. However, some US state statutes require two examinations.

- Legally, all physicians are allowed to determine brain death in most US states. Neurologists, neurosurgeons, and intensive care specialists may have specialized expertise. It seems reasonable to require that all physicians making a determination of brain death be intimately familiar with brain death criteria and have demonstrated competence in this complex examination. Brain death statutes in the United States differ by state and institution. Some US state or hospital guidelines require the examiner to have certain expertise.

The Clinical Evaluation (Neurologic Assessment)

Coma

- Patients must lack all evidence of responsiveness
  Eye opening or eye movement to noxious stimuli is absent. Noxious stimuli should not produce a motor response other than spinally mediated reflexes. The clinical differentiation of spinal responses from retained motor responses associated with brain activity requires expertise.

Absence of Brainstem Reflexes

- Absence of pupillary response to a bright light is documented in both eyes
  Usually the pupils are fixed in a midsize or dilated position (4–9 mm). Constricted pupils suggest the possibility of drug intoxication. When uncertainty exists about reactivity, a magnifying glass should be used.

- Absence of ocular movements using oculocephalic testing and oculovestibular reflex testing
  Once the integrity of the cervical spine is ensured, the head is briskly rotated horizontally and vertically. There should be no movement of the eyes relative to head movement. The oculovestibular reflex is tested by irrigating each ear with ice water (caloric testing) after the patency of the external auditory canal is confirmed. The head is elevated to 30 degrees. Each external auditory canal is irrigated (one ear at a time) with approximately 50 ml of ice water. Movement of the eyes should be absent during 1 minute of observation. Both sides are tested, with an interval of several minutes.

- Absence of corneal reflex
  Absent corneal reflex is demonstrated by touching the cornea with a piece of tissue paper, a cotton swab, or squirts of water. No eyelid movement should be seen.

- Absence of facial muscle movement to a noxious stimulus
  Deep pressure on the condyles at the level of the temporomandibular joints and deep pressure at the supraorbital ridge should produce no grimacing or facial muscle movement.
Absence of the pharyngeal and tracheal reflexes

The pharyngeal or gag reflex is tested after stimulation of the posterior pharynx with a tongue blade or suction device. The tracheal reflex is most reliably tested by examining the cough response to tracheal suctioning. The catheter should be inserted into the trachea and advanced to the level of the carina followed by one or two suctioning passes.

Apnea

Absence of a breathing drive

Absence of a breathing drive is tested with a CO₂ challenge. Documentation of an increase in PaCO₂ above normal levels is typical practice. It requires preparation before the test.

Prerequisites: 1. normotension, 2. normothermia, 3. euvolemia, 4. eucapnia (PaCO₂ 35–45 mm Hg), 5. absence of hypoxia, and 6. no prior evidence of CO₂ retention (i.e., chronic obstructive pulmonary disease, severe obesity).

Procedure

1. Adjust vasopressors to a systolic blood pressure ≥100 mm Hg.
2. Preoxygenate for at least 10 minutes with 100% oxygen to a PaO₂ >200 mm Hg.
3. Reduce ventilation frequency to 10 breaths per minute to eucapnia.
4. Reduce PEEP to 5 cm H₂O (oxygen desaturation with decreasing PEEP may suggest difficulty with apnea testing).
5. If pulse oximetry oxygen saturation remains >95%, obtain a baseline blood gas (partial pressure of oxygen [PaO₂], PaCO₂, pH, bicarbonate, base excess).
6. Disconnect the patient from the ventilator.
7. Preserve oxygenation (e.g., place an insufflation catheter through the endotracheal tube and close to the level of the carina and deliver 100% O₂ at 6 L/min).
8. Look closely for respiratory movements for 8–10 minutes. Respiration is defined as abdominal or chest excursions and may include a brief gasp.
9. Abort if systolic blood pressure decreases to <90 mm Hg.
10. Abort if oxygen saturation measured by pulse oximetry is <85% for >30 seconds. Retry procedure with T-piece, continuous positive airway pressure (CPAP) 10 cm H₂O, and 100% O₂ 12 L/min.
11. If no respiratory drive is observed, repeat blood gas (PaO₂, PaCO₂, pH, bicarbonate, base excess) after approximately 8 minutes.
12. If respiratory movements are absent and arterial PCO₂ is ≥60 mm Hg (or 20 mm Hg increase in arterial PCO₂ over a baseline normal arterial PCO₂), the apnea test result is positive (i.e., supports the clinical diagnosis of brain death).
13. If the test is inconclusive but the patient is hemodynamically stable during the procedure, it may be repeated for a longer period of time (10–15 minutes) after the patient is again adequately preoxygenated.

**Ancillary Tests**

- In clinical practice, EEG, cerebral angiography, nuclear scan, and transcranial Doppler (TCD) are currently used ancillary tests in adults. Most hospitals will have the logistics in place to perform and interpret an EEG, nuclear scan, or cerebral angiogram, and these three tests may be considered the preferred tests. Ancillary tests can be used when uncertainty exists about the reliability of parts of the neurologic examination or when the apnea test cannot be performed. In some protocols, ancillary tests are used to shorten the duration of the observation period.

- The interpretation of each of these tests requires expertise. In adults, ancillary tests are not needed for the clinical diagnosis of brain death and cannot replace a neurologic examination. Physicians ordering ancillary tests should appreciate the disparities between tests and the potential for false-positives (i.e., the test suggests brain death, but the patient does not meet clinical criteria). Rather than ordering ancillary tests, physicians may decide not to proceed with the declaration of brain death if clinical findings are unreliable.

**Documentation**

- The time of brain death is documented in the medical records. Time of death is the time the arterial PCO$_2$ reached the target value. In patients with an aborted apnea test, the time of death is when the ancillary test has been officially interpreted. A checklist (see figure 8) is filled out, signed, and dated. Federal and state law requires the physician to contact an organ procurement organization following determination of brain death.

* Evidence rating key can be found on page 5 of this pocket guide.

**See published guideline for detailed information on methods of ancillary testing.**
Guidelines

The following pages summarize three AAN guidelines on spasticity and/or cerebral palsy (CP):

Pharmacologic Treatment of Spasticity in Cerebral Palsy (*Neurology* 2010;74:336–343)

Botulinum Neurotoxin for the Treatment of Spasticity (*Neurology* 2008;70:1691–1698)


Tools & Resources

Please refer to www.aan.com to access the full guidelines and the following companion tools:

- Clinician Summaries
- Patient/Caregiver Summaries
- Slide Presentations
- Clinical Examples
- Posters
- Podcast

Pharmacologic Treatment of Spasticity in Cerebral Palsy (2010)

This is a summary of the AAN and Child Neurology Society (CNS) guideline on pharmacologic treatment of spasticity in cerebral palsy (CP). Botulinum toxin type A (BoNT-A) was found to be generally safe in children with CP; however, the US Food and Drug Administration (FDA) is presently investigating isolated cases of generalized weakness resulting in poor outcomes.

Recommendations

Localized or Segmental Spasticity

- For localized/segmental spasticity in the upper and lower extremities of children with CP that warrants treatment, BoNT-A should be offered as an effective and generally safe treatment (A*).
- There is insufficient evidence to support or refute the use of BoNT-A to improve motor function in this population (U). There is insufficient evidence to support or refute the use of BoNT-B, phenol, and alcohol injections as a treatment for spasticity in children with spastic CP (U).
- *Clinical Context:* At the time of this writing, the FDA has not approved BoNT-A for the treatment of spasticity in children. BoNT-A is approved for the treatment of spasticity in children and adults in Canada and several other countries. Different formulations are not bioequivalent and may have different therapeutic efficacy and safety profiles. The FDA released a
communication describing some systemic reactions after BoNT injection (A or B) for limb spasticity associated with CP.

**Generalized Spasticity**

- Diazepam should be considered as a short-term antispasticity treatment in children with CP (B).
- There is insufficient evidence to support or refute the use of diazepam to improve motor function in this population (U).
- **Clinical Context:** The incidence of adverse events (AEs) associated with diazepam is an important limiting factor for long-term use. Experts caution that the prolonged use of this medication can produce physical dependence and recommend against abrupt discontinuation.
- There is insufficient evidence to support or refute the use of dantrolene for the treatment of spasticity in children with CP (U).
- **Clinical Context:** Dantrolene is rarely used in clinical practice to reduce spasticity in children with CP. This may be due to the lack of evidence in the literature to support its efficacy and the general concern regarding its potential frequent and/or serious AEs. Although dantrolene has been associated with hepatotoxicity, none of the studies reviewed reported this AE in children, perhaps due to the small number of subjects included in these investigations.
- There is insufficient evidence to support or refute the use of oral baclofen for the treatment of spasticity or to improve motor function in children with CP (U).
- **Clinical Context:** Baclofen is widely used in clinical practice to treat spasticity in children with CP. Experts recommend starting baclofen at the lowest possible dose to minimize AEs. The dose is gradually tapered until discontinuing because abrupt discontinuation may cause withdrawal symptoms.
- Tizanidine may be considered for the treatment of spasticity in children with CP (C).
- There is insufficient evidence to support or refute the use of tizanidine to improve motor function in this population (U).
- **Clinical Context:** Tizanidine’s antispasticity effect has been demonstrated in adults with multiple sclerosis and spinal cord injury. Little information is available to assist practitioners with the effective use of this drug to treat spasticity in children. Because tizanidine is extensively metabolized by the liver, hepatic impairment may have a significant effect on its pharmacokinetics. There are AEs related to tizanidine use in adults. Their incidence in pediatric patients has not been studied.
- There is insufficient evidence to support or refute the use of continuous intrathecal baclofen pump (ITB) for the treatment of spasticity in children with CP (U).
Clinical Context: In 1996, ITB received FDA approval to treat spasticity of cerebral origin. A major factor in the lack of Class I and II evidence may be the difficulty of performing a randomized control trial or crossover trial in subjects with ITB pumps. Catheter-related complications, pump pocket collections, and wound infections remain a concern, and ongoing efforts aim to reduce their incidence. One retrospective study of the safety of ITB in children (N=200) found that 11% had CSF leakage, 7% had catheter-related problems, and 5.5% developed infections.

* Evidence rating key can be found on page 5 of this pocket guide.

Botulinum Neurotoxin for the Treatment of Spasticity (2008)

Endorsed by the American Academy of Physical Medicine and Rehabilitation and the American Association of Neuromuscular and Electrodiagnostic Medicine.

This is a summary of the AAN and the Child Neurology Society (CNS) guideline on diagnostic assessment of cerebral palsy (CP). The ability of botulinum neurotoxin (BoNT) to block acetylcholine release at neuromuscular junctions accounts for its therapeutic action to relieve dystonia, spasticity, and related disorders. This guideline reviewed the evidence for the safety and efficacy of BoNT in the treatment of adult and childhood spasticity.

Recommendations

Botulinum Neurotoxin in Adults with Spasticity

• Strong evidence supports use of botulinum neurotoxin (BoNT) as a treatment option to reduce muscle tone and improve passive function (A*).
• Good evidence supports consideration of BoNT to improve active function (B).
• There is insufficient evidence to recommend an optimum technique for muscle localization at the time of injection (U).
• Clinical Context: There are no controlled studies comparing BoNT to other treatment modalities for spasticity. In adult spasticity, there is a lack of consensus on what constitutes meaningful functional gain following treatment for spasticity. There is also a need to confirm efficacy for active function in controlled trials.

Botulinum Neurotoxin in Children with Spasticity Due to Cerebral Palsy

• Strong evidence supports injection of BoNT into calf muscles as a treatment option for equinus varus deformity in children with cerebral palsy (CP) (A).
• Good evidence supports consideration of BoNT as a treatment option for thigh adductor spasticity and for pain control undergoing adductor-lengthening surgery (B).
• Good evidence supports injection of BoNT as a treatment option for children with upper-extremity spasticity (B).
• Clinical Context: Though clinicians, patients, and caregivers have
found BoNT treatment for spasticity gratifying, the US Food and Drug Administration (FDA) has not approved BoNT for the treatment of spasticity in children or adults.

* Evidence rating key can be found on page 5 of this pocket guide.

**Diagnostic Assessment of the Child with Cerebral Palsy** (2004; reaffirmed 2007)

This is a summary of the AAN guideline on treatment of spasticity in cerebral palsy (CP). The guideline evaluates the value and utility of investigative tests used to evaluate children diagnosed as having CP. The guideline also reviewed evidence pertaining to the frequency of other correlated health issues in children with CP, such as epilepsy, mental retardation, and ophthalmologic and hearing impairments.

**Recommendations**

**Neuroimaging (MRI and CT)**

- Neuroimaging is recommended in the evaluation of a child with CP if the etiology has not been established, for example by perinatal imaging (**A**

- MRI, when available, is preferred to CT scanning because of the higher yield of suggesting an etiology and timing of insult leading to CP (**A**).

**Metabolic and Genetic Testing**

- Metabolic and genetic studies need not be routinely obtained in the evaluation of the child with CP (**B**).

- If the clinical history or findings on neuroimaging do not determine a specific structural abnormality or if there are additional and atypical features in the history or clinical examination, metabolic and genetic testing should be considered (**C**).

- Detection of a brain malformation in a child with CP warrants consideration of an underlying genetic or metabolic etiology (**C**).

**Coagulopathies**

- Because the incidence of unexplained cerebral infarction seen with neuroimaging is high in children with hemiplegic CP, diagnostic testing for a coagulation disorder should be considered (**B**). There is insufficient evidence to be precise as to what studies should be ordered.

**EEG for Epilepsy**

- An EEG should not be obtained for the purpose of determining the etiology of CP (**A**).

- An EEG should be obtained when a child with CP has a history or examination features suggesting the presence of epilepsy or an epileptic syndrome (**A**).
Screening for Mental Retardation, Ophthalmologic and Hearing Impairments, and Speech and Language Disorders

- Because of the high incidence of associated conditions, children with CP should be screened for mental retardation, ophthalmologic and hearing impairments, and speech and language disorders (A). Nutrition, growth, and swallowing should be monitored. Further specific evaluations are warranted if screening suggests areas of impairment.

- There is insufficient evidence to recommend the best sequence of tests to determine the etiology of CP. Taking into account diagnostic yield and potential ability to treat, the AAN developed a consensus-based evaluation algorithm (see figure 9).

Figure 9. Evaluation of the child with CP

<table>
<thead>
<tr>
<th>History and examination findings suggest diagnosis of CP (nonprogressive disorder of motor control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Confirm that the history does not suggest a progressive or degenerative central nervous system disorder.</td>
</tr>
<tr>
<td>2. Assure that features suggestive of progressive or degenerative disease are not present on examination.</td>
</tr>
<tr>
<td>3. Classify the type of CP (quadriplegia, hemiplegia, diplegia, ataxic, etc). For the most part this classification system is one of convenience, i.e., easy communication. It does not necessarily relate to prognosis or to what treatments are indicated.</td>
</tr>
<tr>
<td>4. Screen for associated conditions including:</td>
</tr>
<tr>
<td>- Developmental delay/mental retardation</td>
</tr>
<tr>
<td>- Ophthalmologic/hearing impairments</td>
</tr>
<tr>
<td>- Speech and language delay</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Did the child have previous neuroimaging or other laboratory studies (e.g., in neonatal period) that determined the etiology of CP?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>No need for further diagnostic testing</td>
</tr>
<tr>
<td>Normal MRI</td>
</tr>
</tbody>
</table>

1. Consider metabolic or genetic testing if upon follow-up the child has:
- Evidence of deterioration or episodes of metabolic decompensation
- No etiology determined by medical evaluation
- Family history of childhood neurologic disorder associated with CP

1. Determine if neuroimaging abnormalities in combination with history and examination establishes a specific etiology of CP
2. If developmental malformation is present, consider genetic evaluation
3. If previous stroke, consider evaluation for coagulopathy or other etiology

*Evidence rating key can be found on page 5 of this pocket guide.*
Guideline
This is a summary of the AAN guideline update on evaluation and management of driving risk in dementia (*Neurology* 2010;74:1316–1324).

Tools & Resources
Please refer to [www.aan.com](http://www.aan.com) to access the full guideline update and the following companion tools:

- Clinician Summary
- Patient/Caregiver Summary
- Slide Presentation
- Clinical Example
- Poster
- Video
- Podcast
- Background/Data

Summary
While patients with mild dementia, as a group, are higher-risk drivers, more recent studies report that as many as 76% are still able to pass an on-road driving test (ORDT) and can safely drive. Faced with these facts, clinicians caring for patients with dementia seek to identify those patients with cognitive impairment who may be at higher risk for unsafe driving, without unnecessarily restricting those who are safe drivers. This update of the 2000 AAN guideline on driving and dementia seeks to identify factors that are associated with increased driving risk.

Update: Evaluation and Management of Driving Risk in Dementia (2010)

Recommendations

Global Measures of Dementia Severity

- For patients with dementia, the Clinical Dementia Rating (CDR) scale is established as useful for identifying patients at increased risk for unsafe driving (A*).
- For patients with dementia, Mini-Mental State Examination (MMSE) scores of ≤24 may be considered useful for identifying patients at increased risk for unsafe driving (C).

Patient Self-Assessment/Caregiver Assessment

- For patients with dementia, a patient’s self-rating of “safe” driving ability is established as not useful for identifying patients at increased risk for unsafe driving (A).
- For patients with dementia, a caregiver’s rating of a patient’s driving ability as “marginal” or “unsafe” should be considered useful for identifying patients at increased risk for unsafe driving (B).
Driving History

- A history of traffic citations may be considered useful for identifying patients at increased risk for unsafe driving (C).
- A history of crashes may be considered useful for identifying patients at increased risk for unsafe driving (C).
- For patients with dementia, reduced driving mileage may be considered useful for identifying patients at increased risk for unsafe driving (C).
- Self-reported situational avoidance may be considered useful for identifying patients at increased risk for unsafe driving (C).
- Lack of situational avoidance may be considered as not useful for identifying patients at increased risk for unsafe driving (C).
- Aggressive or impulsive personality characteristics may be considered useful for identifying patients at increased risk for unsafe driving (C).

Neuropsychological Tests

- There is insufficient evidence to support or refute the benefit of neuropsychological testing, after controlling for the presence of dementia, for drivers with dementia (U).

Interventions

- There is insufficient evidence to support or refute the benefit of interventional strategies for drivers with dementia (U).

Clinical Context

- Clinicians are obligated to identify conditions that may risk their patients’ or the public’s health. Because there is no test result or historical feature that accurately quantifies driving risk, clinicians can make only qualitative estimates of driving risk. Clinicians may present data showing that patients with mild dementia (CDR of 1) are at a substantially higher risk for unsafe driving and thus should strongly consider discontinuing driving. However, advocates for maintaining driving privileges may cite the wide confidence intervals for relative risk and ORDT pass rates of 41% to 76% as evidence against a categorical recommendation for these patients to cease driving. Such advocates do not want truly capable drivers to cease driving prematurely. In that case, one may look for evidence of increased risk in an individual patient. Consideration of these additional issues can result in a more accurate prediction of driving performance.

- A clinician may wish to integrate this information into an algorithm (see figure 10) to obtain a qualitative estimate of driving risk. This algorithm should only be considered supplementary to the clinician’s judgment. Patients at higher risk may agree to surrender privileges. For those who wish to continue driving, clinicians may consider referral for a professional or governmental driving evaluation, depending on state reporting laws. Patients who continue to drive should be reassessed at 6-month intervals. Neuropsychological testing offers a means of assessing memory, spatial
cognition, and executive functioning that is more sensitive than the MMSE or CDR, while it seems intuitive that a more accurate determination of impairment in specific cognitive domains would result in a more accurate estimate of driving risk, there are no data at this time to support or refute this approach. Additional medical conditions also may be relevant, but those issues are beyond the scope of this review.

• Qualitative risk estimates are a familiar part of clinical practice. However, clinicians may be less comfortable making such judgments in a legal context. When the threshold for “likely” impairment is low or unclear, some clinicians may choose to report borderline cases. In some states, doing so may leave them open to civil litigation. This guideline cannot operationalize these types of subjective statutory requirements; it is intended for use in a clinical setting to assist in an evidence-based estimate of driving risk.

Figure 10. Sample algorithm for evaluating driving competence and risk management in patients with dementia

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>CDR 0.5–1.0</th>
<th>CDR 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluate for risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level B evidence</td>
<td>Caregiver report of marginal or unsafe skills</td>
<td></td>
</tr>
<tr>
<td>Level C evidence</td>
<td>History of citations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of crashes</td>
<td></td>
</tr>
<tr>
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<td>Driving &lt; 60 miles/week</td>
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<tr>
<td></td>
<td>Situational avoidance</td>
<td></td>
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<tr>
<td></td>
<td>Aggression, impulsivity</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Alcohol, medications, sleep disorders, visual impairment, motor impairment</td>
<td></td>
</tr>
</tbody>
</table>

Risk factors:
- None
- Few
- Several
- Multiple

Relatively low risk
- Encourage family support for alternate transportation.
- Strongly consider voluntary surrender of driving privileges.
- Consider DMV referral or professional driving evaluation, based on state guidelines.

Relatively high risk
- Intervention pursuant to state guidelines

See the published guideline for the scoring rubric of the Clinical Dementia Rating scale and for Patient and Family/Caregiver Questionnaires.

* Evidence rating key can be found on page 5 of this pocket guide.
Guideline

This is a summary of the AAN and the Child Neurology Society (CNS) guideline assessing corticosteroid treatment of Duchenne muscular dystrophy (DMD) (Neurology 2005;64:13–20; reaffirmed February 2008).

Tools & Resources

Please refer to www.aan.com to access the full guideline and the following companion tools:

- Clinician Summary
- Patient/Caregiver Summary
- Slide Presentation

Summary

The guideline concludes that prednisone has been demonstrated to have a beneficial effect on muscle strength and function in boys with DMD and should be offered as treatment. Benefits and side effects of corticosteroid therapy need to be monitored, and the offer of treatment with corticosteroids should include a balanced discussion of potential risks. Deflazacort can also be used for the treatment of DMD in countries in which it is available.

Corticosteroid Treatment of Duchenne Dystrophy (2005; reaffirmed 2008)

Recommendations

- Prednisone has been demonstrated to have a beneficial effect on muscle strength and function in boys with DMD and should be offered (at a dose of 0.75 mg/kg/d) as treatment (A*). Maintaining a dosage of 0.75 mg/kg/d is optimal; however, if side effects require a decrease in prednisone, tapering to dosages as low as 0.3 mg/kg/d gives less robust but significant improvement (A).

- Benefits and side effects of corticosteroid therapy need to be monitored. Timed function tests, pulmonary function tests, and age at loss of independent ambulation are useful to assess benefits. An offer of treatment with corticosteroids should include a balanced discussion of potential risks. Potential side effects of corticosteroid therapy (weight gain, cushingoid appearance, cataracts, short stature [i.e., a decrease in linear growth], acne, excessive hair growth, gastrointestinal symptoms, and behavioral changes) also need to be assessed. If excessive weight gain occurs (>20% over estimated normal weight for height over a 12-month period), on the basis of available data it is recommended that the dosage of prednisone be decreased (to 0.5 mg/kg/d with a further decrease after 3 to 4 months to 0.3 mg/kg/d if excessive weight gain continues) (A).
• Deflazacort (0.9 mg/kg/d) can also be used for the treatment of DMD in countries in which it is available (A). Patients should be monitored for asymptomatic cataracts as well as weight gain during treatment with deflazacort (A).

* Evidence rating key can be found on page 5 of this pocket guide.
**Guidelines**

The following pages summarize ten AAN guidelines on epilepsy or first seizure:


Diagnostic Assessment of the Child with Status Epilepticus (Neurology 2006;67:1542–1550; reaffirmed July 2010)

Use of Serum Prolactin in Diagnosing Epileptic Seizures (Neurology 2005;65:668–675; reaffirmed November 2008)

Surgical Management of Epilepsy (Neurology 2003;60:538–547; reaffirmed October 2005)

Treating a First Unprovoked Seizure in Children (Neurology 2003;60:166–175; reaffirmed July 2006 and July 2010)


**Tools & Resources**

Please refer to [www.aan.com](http://www.aan.com) to access the full guidelines, guideline updates, and the following companion tools:

- Clinician Summaries
- Patient/Caregiver Summaries
- Patient/Caregiver Summary Translations
- Slide Presentations
- Videos
- Clinical Examples
- Podcasts
- Posters
- Background/Data

This is a summary of the AAN and American Epilepsy Society guideline regarding management and care of women with epilepsy (WWE) during pregnancy. Recommendations are presented for obstetric or other health complications, change in seizure frequency, risk of status epilepticus, and rate of continued seizure freedom during pregnancy.

**Recommendations**

**Obstetrical Complications**

- Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is probably no substantially increased risk (greater than 2 times expected) of cesarean delivery for WWE taking antiepileptic drugs (AEDs) (B*).
- Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is possibly a moderately increased risk (up to 1.5 times expected) of cesarean delivery for WWE taking AEDs (C).
- Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is probably no substantially increased risk (greater than 2 times expected) of late pregnancy bleeding for WWE taking AEDs (B).
- Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is probably no moderately increased risk (greater than 1.5 times expected) of premature contractions or premature labor and delivery for WWE taking AEDs (B).
- Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is possibly a substantially increased risk of premature contractions and premature labor and delivery during pregnancy for WWE who smoke (C).
- Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is insufficient evidence to support or refute an increased risk of preeclampsia, pregnancy-related hypertension, or spontaneous abortion (U).

**Epilepsy-Related Complications**

- Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that seizure freedom for at least 9 months prior to pregnancy is probably associated with a high likelihood (84%–92%) of remaining seizure free during pregnancy (B).
- Counseling of WWE who are pregnant or are contemplating pregnancy should reflect that there is insufficient evidence to support or refute an increased risk of a change in seizure frequency or status epilepticus (U).
Clinical Context

- There was no conclusive evidence of an increased risk of many obstetrical complications often associated with WWE during pregnancy. This raises the possibility that there is no true difference in the rates of obstetrical complications in WWE compared to the general population.
- Further, the findings do not suggest high rates of status epilepticus, increased seizure rate, or increased risk of seizure relapse during pregnancy for WWE who are seizure free. The available data indicate that seizure-free WWE will remain seizure free during pregnancy, which is another reason to strive for seizure freedom in WWE planning pregnancy.

* Evidence rating key can be found on page 5 of this pocket guide.


This is a summary of the AAN and American Epilepsy Society guideline on management and care of women with epilepsy (WWE) during pregnancy. Recommendations are presented for risk of major congenital malformations (MCMs) associated with intrauterine exposure to antiepileptic drugs (AEDs) in neonates born to WWE, risk of adverse long-term cognitive outcomes in children born to WWE, and risk of death, low birth weight, and low Apgar scores in neonates born to WWE.

Recommendations

Major Congenital Malformations

- If possible, avoidance of the use of valproate (VPA) as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of MCMs (B*).
- If possible, avoidance of the use of VPA monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs (C).
- To reduce the risk of MCMs, the use of VPA during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine (CBZ) (A).
- To reduce the risk of MCMs, avoidance of the use of polytherapy with VPA during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without VPA (B).
- To reduce the risk of MCMs, avoidance of the use of VPA during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin (PHT) or lamotrigine (LTG) (C).
- To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered (B).
• Limiting the dosage of VPA or LTG during the first trimester, if possible, should be considered to lessen the risk of MCMs (B).

• Avoidance of the use of VPA, if possible, should be considered to reduce the risk of neural tube defects and facial clefts (B).

• Avoidance of the use of VPA, if possible, may be considered to reduce the risk of hypospadias (C).

• Avoidance of PHT, CBZ, and phenobarbital (PB), if possible, may be considered to reduce the risk of specific MCMs: cleft palate for PHT use, posterior cleft palate for CBZ use, and cardiac malformations for PB use (C).

• Although there is evidence that AEDs taken during the first trimester probably increase the risk of MCMs in the offspring of WWE, it cannot be determined if the increased risk is imparted from all AEDs or from only one or some AEDs. Therefore, no recommendation is made from this conclusion (U).

Cognitive Teratogenesis

• Counseling of WWE who are contemplating pregnancy should reflect that there is probably no increased risk of reduced cognition in the offspring of WWE not taking AEDs (B).

• CBZ exposure probably does not produce cognitive impairment in offspring of WWE (B).

• Avoiding VPA in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes (B).

• Avoiding PHT in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes (C).

• Avoiding PB in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes (C).

• Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy, to reduce the risk of poor cognitive outcomes (B).

• For WWE who are pregnant, avoidance of VPA, if possible, should be considered, compared to CBZ to reduce the risk of poor cognitive outcomes (B).

• For WWE who are pregnant, avoidance of VPA, if possible, may be considered compared to PHT to reduce the risk of poor cognitive outcomes (C).

Adverse Perinatal Outcomes

• Pregnancy risk stratification should reflect that the offspring of WWE taking AEDs during pregnancy probably have an increased risk of smallness for gestational age (SGA). Further, AED use in WWE during pregnancy should be considered in the differential diagnosis of SGA in their offspring (B).

• Pregnancy risk stratification should reflect that neonates born to WWE probably do not have a substantially increased risk of perinatal death (B).

• Pregnancy risk stratification should reflect that the offspring of WWE taking
AEDs during pregnancy possibly have an increased risk of 1-minute Apgar scores of <7. Further, AED use in WWE during pregnancy may be considered in the differential diagnosis of a 1-minute Apgar score of <7 in their offspring (C).

Clinical Context

- AEDs can prevent seizures during pregnancy, which by extension protects the fetus. For most WWE, discontinuing AEDs during pregnancy is not a reasonable or safe option; it may expose the mother and fetus to physical injury from seizure-related accidents.

- It seems reasonable to switch WWE of childbearing potential to a less teratogenic regimen when possible. VPA, although effective, emerges as the AED with the greatest number of data associating it with risk from in-utero exposure. It seems that changing from VPA to another AED should be done well before pregnancy. Changing to another AED during pregnancy poses risk of allergy, other serious adverse reactions, and polytherapy exposure. Changing from VPA several weeks into gestation will not avoid the risk of MCMs, as MCMs develop very early in pregnancy.

- The studies of many AEDs were too small to make conclusions, and the teratogenicity of these drugs is unknown.

- MCMs seen more frequently with VPA, such as neural tube defects, can also be present with exposure to other AEDs, demonstrating that this is not an AED-specific MCM. Like other teratogens, AEDs produce a pattern of MCMs with overlap amongst the individual AEDs.

* Evidence rating key can be found on page 5 of this pocket guide.


This is a summary of the AAN and American Epilepsy Society guideline on management and care of women with epilepsy (WWE) during pregnancy. Recommendations are presented for prenatal folic acid use, prenatal vitamin K use, risk of hemorrhagic disease of the newborn, clinical implications of placental and breast milk transfer of antiepileptic drugs (AEDs), risks of breastfeeding, and change in AED levels during pregnancy.

Recommendations

Risks to Newborns/Neonates

- Preconceptional folic acid supplementation in WWE may be considered to reduce the risk of major congenital malformations (MCMs) (C*).

  Clinical Context: Folic acid supplementation is generally recommended to reduce the risk of MCMs during pregnancy, and although the data are insufficient to show that it is effective in WWE, there is no evidence
of harm and no reason to suspect that it would not be effective in this
group. Therefore, all women of childbearing potential, with or without
epilepsy, should be encouraged to take at least 0.4 mg of folic acid daily
prior to conception and during pregnancy. There was insufficient published
information to address the dosing of folic acid.

- Counseling of WWE who are pregnant or are contemplating pregnancy
  should reflect that there is insufficient evidence to support or refute an
  increased risk of hemorrhagic complications in the newborns of WWE
taking AEDs (U).

- There is insufficient evidence to support or refute a benefit of prenatal
  vitamin K supplementation for reducing the risk of hemorrhagic
  complications in the newborns of WWE (U).

- Clinical Context: Newborns exposed to enzyme-inducing AEDs in utero
typically receive vitamin K at delivery, as is the routine practice for all
newborns.

- The fact that phenobarbital (PB), primidone (PRM), phenytoin (PHT),
carbamazepine (CBZ), levetiracetam (LVT), and valproate (VPA) cross the
placenta may be factored into the clinical decision regarding the necessity of
AED treatment for a woman with epilepsy (B).

- The fact that gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OXC),
and topiramate (TPM) cross the placenta may be factored into the clinical
decision regarding the necessity of AED treatment for a woman with
epilepsy (C).

- VPA, PB, PHT, and CBZ may be considered as not transferring into breast
milk to as great an extent as PRM and LVT (B).

- VPA, PB, PHT, and CBZ may be considered as not transferring into breast
milk to as great an extent as GBP, LTG, and TPM (C).

- Clinical Context: Because of small sample size, there was no way to analyze
the potential contribution of other clinical factors, such as AED polytherapy,
on the passive transfer of AEDs to newborns of WWE.

- No recommendation has been made as to whether indirect exposure to
maternally ingested AEDs leads to symptomatic effects in the newborn (U).

- Clinical Context: Certainly many of the AEDs cross through the placenta
or into breast milk in measurable concentrations, with some meaningful
differences in AEDs. The clinical consequences for the newborn of ingesting
AEDs via breast milk remain sorely underexplored.

Change in AED Levels

- Monitoring of LTG, CBZ, and PHT levels during pregnancy should be
considered (B).

- Monitoring of LVT and OXC (as a monohydroxy derivative [MHD]) levels
during pregnancy may be considered (C).

- There is insufficient evidence to support or refute a change in PB, VPA,
PRM, or ethosuximide (ESM) levels related to pregnancy (U), and this lack of
evidence should not discourage monitoring levels of these AEDs during pregnancy.

• Clinical Context: The studies reviewed provide some evidence supporting active monitoring of AED levels during pregnancy, particularly of LTG, as changes in LTG levels were associated with increased seizure frequency. It seems reasonable to individualize this monitoring for each patient, with the aim of maintaining a level near the preconceptional level, presumably at which the woman with epilepsy was doing well with seizure control.

* Evidence rating key can be found on page 5 of this pocket guide.

Evaluating a First Unprovoked Seizure in Adults (2007)

This is a summary of the AAN and American Epilepsy Society guideline on evaluating first seizure in adults. One major study estimates the annual cost of epilepsy in the United States as having been $12.5 billion in 1995, with the majority of direct cost attributed to diagnostic tests, medical care, and drugs prescribed at the time of the initial evaluation for a seizure disorder or epilepsy. Misdiagnosis may lead to ineffective management choices and excessive and unnecessary costs. Not only are errors expensive, but they may also result in harm to the patient. This guideline focuses on the methods and procedures that complement the standard initial history, physical, and neurologic examination.

Recommendations

EEG

• An EEG should be considered as part of the routine neurodiagnostic evaluation of the adult with an apparent unprovoked first seizure because it has a substantial yield (B*) and because it has value in determining the risk for seizure recurrence (B).

Neuroimaging Studies (CT or MRI)

• Brain imaging using CT or MRI should be considered as part of the routine neurodiagnostic evaluation of adults presenting with an apparent unprovoked first seizure (B).

Laboratory Studies, Lumbar Puncture, and Toxologic Screening

• In the adult initially presenting with an apparent unprovoked first seizure, blood glucose, blood counts, and electrolyte panels (particularly sodium) may be helpful in specific clinical circumstances; lumbar puncture may be helpful in specific clinical circumstances, such as patients who are febrile; and toxicologic screening may be helpful in specific clinical circumstances. But there are insufficient data to support or refute routine recommendation of any of these tests (U).

* Evidence rating key can be found on page 5 of this pocket guide.

This is a summary of the reassessment of the 1996 AAN guideline that evaluated the usefulness of performing an immediate neuroimaging procedure in the emergency department on persons presenting with seizures.

**Recommendations**

- An emergency head CT may be considered in adults with first seizure (C*).
- An emergency head CT may be considered in children with a first seizure (C).
- No recommendation is made regarding an emergency head CT in persons with chronic seizures (U).
- An emergency head CT may be considered in children less than 6 months of age and in patients with AIDS (C).
- An emergency CT should be considered in patients presenting with seizure in the emergency department who have an abnormal neurologic examination, predisposing history, or focal seizure onset (B).

* Evidence rating key can be found on page 5 of this pocket guide.

Diagnostic Assessment of the Child with Status Epilepticus (2006; reaffirmed 2010)

This is a summary of the AAN and Child Neurology Society (CNS) guideline on assessment of status epilepticus (SE) in children. SE in children, as in adults, is a life-threatening emergency that requires prompt recognition and immediate treatment. In the United States, SE occurs in over 30,000 children annually. This guideline provides recommendations for the value of diagnostic testing in children and adolescents with SE. Treatment guidelines are not included but are under development.

**Definition of SE**

Although various definitions of SE have been used since 1983, the most commonly accepted is a 30-minute duration of seizures. This definition also includes two or more sequential seizures without full recovery of consciousness between seizures.

**Recommendations**

**Laboratory Studies**

- There are insufficient data to support or refute whether blood cultures should be done on a routine basis in children in whom there is no clinical suspicion of infection (U*).
- There are insufficient data to support or refute whether lumbar puncture (LP) should be done on a routine basis in children in whom there is no clinical
suspicion of a CNS infection (U).

- Antiepileptic drug (AED) levels should be considered when a child with epilepsy on AED prophylaxis develops SE (B).

- Toxicology testing may be considered in children with SE, when no apparent etiology is immediately identified, as the frequency of ingestion as a diagnosis was at least 3.6% (C). To detect a specific ingestion, suspected because of the clinical history, it should be noted that a specific serum toxicology level is required, rather than simply urine toxicology screening.

**Metabolic and Genetic Testing**

- Studies for inborn errors of metabolism may be considered when the initial evaluation reveals no etiology, especially if there is a preceding history suggestive of a metabolic disorder (C). The specific studies obtained are dependent on the history and the clinical examination. There is insufficient evidence to support or refute whether such studies should be done routinely (U).

- There are insufficient data to support or refute whether genetic testing (chromosomal or molecular studies) should be done routinely in children with SE (U).

**EEG**

- An EEG may be considered in a child presenting with new-onset SE, as it may determine whether there are focal or generalized abnormalities that may influence diagnostic and treatment decisions (C).

- Although nonconvulsive status epilepticus (NCSE) occurs in children who present with SE, there are insufficient data to support or refute recommendations regarding whether an EEG should be obtained to establish this diagnosis (U).

- An EEG may be considered in a child presenting with SE if the diagnosis of pseudostatus epilepticus is suspected (C).

**Neuroimaging Studies**

- Neuroimaging may be considered for the evaluation of the child with SE if there are clinical indications or if the etiology is unknown (C). If neuroimaging is done, it should only be done after the child is appropriately stabilized and the seizure activity controlled.

- There is insufficient evidence to support or refute recommending routine neuroimaging (U).

* Evidence rating key can be found on page 5 of this pocket guide.

**Use of Serum Prolactin in Diagnosing Epileptic Seizures** (2005; reaffirmed 2008)

This is a summary of the AAN guideline on serum prolactin in diagnosing epileptic seizures. Most studies used a serum prolactin (PRL) of at least twice baseline value as abnormal. For the differentiation of epileptic seizures...
from psychogenic nonepileptic seizures, one Class I and seven Class II studies showed that elevated serum PRL was highly predictive of either generalized tonic–clonic (GTC) or complex partial seizures (CPSs). Pooled sensitivity was higher for GTC seizures (60.0%) than for CPSs (46.1%), while the pooled specificity was similar for both (approximately 96%). Data were insufficient to establish validity for simple partial seizures. Two Class II studies were consistent in showing PRL elevation after tilt-test–induced syncope. Inconclusive data exist regarding the value of serum PRL following status epilepticus, repetitive seizures, and neonatal seizures.

**Recommendations**

- Elevated serum PRL, when measured in appropriate clinical setting at 10 to 20 minutes after a suspected event, should be considered a useful adjunct to differentiate GTC seizure or CPS from psychogenic nonepileptic seizure among adults and older children (B*).
- Serum PRL, when measured more than 6 hours after a suspected event, should be representative of the baseline PRL level (B).
- Serum PRL assay is not of utility to distinguish seizure from syncope (B).
- The utility of serum PRL assay has not been established in the evaluation of status epilepticus, repetitive seizures, or neonatal seizures (U).

* Evidence rating key can be found on page 5 of this pocket guide.

**Surgical Management of Epilepsy** (2003; reaffirmed 2005)

- This is a summary of the AAN and American Association of Neurologic Surgeons (AANS) guideline on surgical management of epilepsy. Evidence indicates that the benefits of anteromesial temporal lobe resection as a treatment for disabling complex partial seizures (CPSs) in appropriately selected patients are greater than continued treatment with antiepileptic drugs (AEDs), and the risks are at least comparable.
- Approximately two-thirds of patients become free of seizures, excepting simple partial seizures, after anterior temporal lobectomy; 10% to 15% are unimproved after surgery.
- Quality of life is significantly better in patients who are seizure free.
- Psychiatric outcome and neuropsychologic and psychosocial function after surgery can improve or worsen, with worsening related predominantly to persistence of seizures.
- Employment status and activities of daily living in general improve, mortality is decreased, and medication regimens are reduced after surgery.
- This evaluation does not address the efficacy of surgical intervention for specific types of epilepsy or underlying pathological substrates. Nor does it evaluate the localizing or prognostic value of presurgical diagnostic tests or strategies. There were insufficient data in the literature to permit
definitive evidence-based conclusions regarding the safety and efficacy of a number of other surgical interventions that are now commonly practiced, including multilobar resections, hemispherectomies, corpus callosotomies, lesionectomies, and multiple subpial transections. Furthermore, the data do not permit conclusions about when surgery should be considered.

Recommendations

- Patients with disabling CPSs, with or without secondarily generalized seizures, who have failed appropriate trials of first-line AEDs should be considered for referral to an epilepsy surgery center, although criteria for failure of drug treatment have not been definitely established (A*).

- Patients referred to an epilepsy surgery center for the reasons stated above and who both meet established criteria for an anteromesial temporal lobe resection and accept the risks and benefits of this procedure, as opposed to continuing pharmacotherapy, should be offered surgical treatment (A).

- There is insufficient evidence at this time to make a definitive recommendation as to whether patients with a localized neocortical epileptogenic region will or will not benefit from surgical resection (U).

* Evidence rating key can be found on page 5 of this pocket guide.

Treating a First Unprovoked Seizure in Children (2003; reaffirmed 2006 and 2010)

- This is a summary of the AAN and Child Neurology Society (CNS) guideline on treating first seizure in children. The decision as to whether or not to treat with antiepileptic drugs (AEDs) following a first unprovoked seizure in a child or adolescent must be based on a risk–benefit assessment which weighs the risk of another seizure (both the statistical risk of recurrence and the potential consequences of a recurrence) against the risk (cognitive, behavioral, and physical as well as psychosocial) of chronic AED therapy. This decision must be individualized and take into account both medical issues and patient and family preference.

- The majority of children who experience a first unprovoked seizure will have few or no recurrences. Only approximately 10% will go on to have many (10 or more) seizures regardless of therapy. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission (Class II). In several studies combining children and adults, treatment has been shown to reduce the risk of seizure recurrence. There is a relative paucity of data from studies involving only children after a first seizure.

- AED therapy in children who have epilepsy (at least two seizures) has potential serious pharmacological and psychosocial side effects (Class I). No separate data exist specifically for treatment of side effects in children who have experienced only a single seizure. There is no evidence about whether treatment specifically after the first seizure alters the risk of SUDEP (sudden, unexpected death of a patient with epilepsy) in children.
Epilepsy and First Seizure

**Recommendations**

- Treatment with AEDs is not indicated for the prevention of the development of epilepsy (B*).
- Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacological and psychosocial side effects (B).

* Evidence rating key can be found on page 5 of this pocket guide.


This is a summary of the AAN and Child Neurology Society guideline on evaluating a first nonfebrile seizure in children. This guideline addresses the evaluation of children aged 1 month to 21 years who have experienced a first nonfebrile seizure that cannot be explained by an immediate, obvious provoking cause such as head trauma or intracranial infection.

**Recommendations**

**Laboratory Studies**

- Laboratory tests should be ordered on the basis of individual clinical circumstances that include suggestive historic or clinical findings such as vomiting, diarrhea, dehydration, or failure to return to baseline alertness (C*).
- Toxicology screening should be considered across the entire pediatric age range if there is any question of drug exposure or substance abuse (C).

**Lumbar Puncture**

- In the child with a first nonfebrile seizure, lumbar puncture (LP) is of limited value and should be used primarily when there is concern about possible meningitis or encephalitis (C).

**EEG**

- The EEG is recommended as part of the neurodiagnostic evaluation of the child with an apparent first unprovoked seizure (A).

**Neuroimaging Studies**

- If a neuroimaging study is obtained, MRI is the preferred modality (B).
- Emergent neuroimaging should be performed in a child of any age who exhibits a postictal focal deficit (Todd's paresis) not quickly resolving, or who has not returned to baseline within several hours after the seizure (C).
- Nonurgent imaging studies with MRI should be seriously considered in any child with a significant cognitive or motor impairment of unknown etiology, unexplained abnormalities on neurologic examination, a seizure of partial (focal) onset with or without secondary generalization, an EEG that does not represent a benign partial epilepsy of childhood or primary generalized epilepsy, or in children under 1 year of age (C).

* Evidence rating key can be found on page 5 of this pocket guide.
Guideline
This is a summary of the AAN guideline on assessing patients in a neurology practice for risk of falls (Neurology 2008;70:473–479).

Tools & Resources
Please refer to www.aan.com to access the full guideline and the following companion tools:

- Clinician Summary
- Patient/Caregiver Summary
- Slide Presentation
- Clinical Example
- Poster
- Podcast
- Get-Up-and-Go Test
- Timed Up-and-Go Test

Summary
Because many patients at risk of falling seek neurologic consultations, neurologists have the opportunity to identify those at greatest risk, document risk factors, and offer interventions that may prevent falls among patients with chronic neurologic disease.


Conclusions

Falls Risk: Established Predictors
- Diagnoses of stroke, dementia, disorders of gait and balance, and people who use assistive devices to ambulate (A*)
- A history of recent falls (A)

Falls Risk: Probable Predictors
- Parkinson disease, peripheral neuropathy, lower extremity weakness or sensory loss, and substantial loss of vision (B)

Screening Instruments
- Additional screening instruments of probable value include the Get-Up-and-Go Test or Timed Up-and-Go Test, an assessment of ability to stand from a sitting position, and the Tinetti Mobility Scale (B).
- Other screening instruments of possible utility are described in appendix e-4, which is available in supplemental data available at www.neurology.org (C).
- Some screening measures assess similar or overlapping neurologic functions—i.e., gait, mobility, and balance—and there is insufficient evidence to assess whether such measures offer benefits beyond that offered by a standard comprehensive neurologic examination (U).
- Other systematic, evidence-based reviews of numerous studies have identified general risk factors for falls, including advanced age,
age-associated frailty, arthritis, impairments in activities of daily living, depression, and the use of psychoactive medications, including sedatives, antidepressants, and neuroleptics.

**Recommendations**

- All of the patients with any of the falls risk factors described in the guideline should be asked about falls during the past year (A).
- After a comprehensive standard neurologic examination, including an evaluation of cognition and vision, if further assessment of the extent of fall risk is needed, other screening measures to be considered include the Get-Up-and-Go Test or Timed Get-Up-and-Go Test, an assessment of ability to stand unassisted from a sitting position, and the Tinetti Mobility Scale (B).
- Other screening measures of possible utility described in appendix e-4, which is available in supplemental data available at www.neurology.org, may be considered (C).

**Clinical Context**

- Interventions to reduce identified fall risks are beyond the scope of this guideline. However, other evidence-based guidelines for the management of these risks have been developed that may be consulted, as well as guidelines for the treatment of underlying disorders where possible.
- Figure 11 presents an algorithm for assessing risk of falls and managing patients at risk.
**Figure 11. Suggested key elements for assessing risk of falls and managing patients at risk**

A. Inquire about falls in past year *(Level A)*

And:

B. Review history for risk factors for falling

**Neurologic: (Levels A & B)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tr>
<td>Stroke</td>
<td>Parkinsonism</td>
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<tr>
<td>Dementia</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Gait or mobility problem</td>
<td>Use of assistive device</td>
</tr>
<tr>
<td>General: (Not rated)</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>Depression</td>
</tr>
<tr>
<td>Vision deficit</td>
<td>Polypharmacy</td>
</tr>
<tr>
<td>Arthritis, arthralgia</td>
<td></td>
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</tbody>
</table>

IF A or B positive

C. Evaluate neurologic function:

a. Neurologic examination, emphasizing:
   - balance and gait *(Level A)*
   - LE strength, sensation & coordination *(Level A)*
   - mental status *(Level A)*

b. In addition, may consider a standardized assessment *(Levels B & C)*

And consider clinical context:

D. Management may address:

a. Underlying disorder
b. Adjustment of medication
c. Exercise program
d. Training in gait and balance
e. Training in assistive device
f. Assessment/modification of home environment

(according to established evidence-based guidelines)

* Evidence rating key can be found on page 5 of this pocket guide.
Guideline

This is a summary of the AAN guideline on Guillain-Barré syndrome (GBS) (Neurology 2003;61:736–740; reaffirmed October 2005 and August 2008).

Tools & Resources

Please refer to www.aan.com to access the full guideline and the following companion tools:

- Clinician Summary
- Slide Presentation
- Background/Data
- Patient/Caregiver Summary

Summary

Treatment with plasma exchange (PE) or IV immunoglobulin (IVIg) hastens recovery from GBS. Combining the two treatments is not beneficial. Steroid treatment given alone is not beneficial.


Recommendations

Plasma Exchange

- PE is recommended in nonambulant patients within 4 weeks of onset of neuropathic symptoms (A*).
- PE is recommended for ambulant patients within 2 weeks of onset of neuropathic symptoms (B).
- If PE started within 2 weeks of onset, there are equivalent effects of PE and IVIg in patients requiring walking aids (B).
- PE is a treatment option for children with severe GBS (B).

IV Immunoglobulin

- IVIg is recommended in nonambulant patients within 2 weeks (A) or 4 weeks (B) of onset of neuropathic symptoms.
- If started within 2 weeks of onset, IVIg has comparable efficacy to PE in patients requiring walking aids (B).
- IVIg is a treatment option for children with severe GBS (B).
- Multiple complications were significantly less frequent with IVIg than with PE (Class I evidence).

Combined Treatments

- Sequential treatment with PE followed by IVIg does not have a greater effect
than either treatment given alone (A).

• There is insufficient evidence to support or refute immunoabsorption treatment followed by IVIg (U).

Corticosteroids

• Steroids are not recommended in the treatment of GBS (A).

Cerebrospinal Fluid Filtration

• There is insufficient evidence to support or refute the use of cerebrospinal fluid (CSF) filtration (U).

Immunoabsorption

• The evidence is insufficient to support or refute immunoabsorption as an alternative to PE (U).

* Evidence rating key can be found on page 5 of this pocket guide.
Guidelines
The following pages summarize four AAN guidelines on headache or migraine headache:


Pharmacological Treatment of Migraine Headache in Children and Adolescents (Neurology 2004;63:2215–2224)


Tools & Resources
Please refer to www.aan.com to access the full guideline and the following companion tools:

• Clinician Summary  • Patient/Caregiver Summary  • Slide Presentation


• This is a summary of an addendum to the AAN guideline “Prevention of Post-Lumbar Puncture Headache” (Neurology 2000;55:909–914).

• Review of the literature on prevention of post-lumbar puncture headaches (PLPHAs) since the publication of the original assessment in 2000 yielded one study comparing use of cutting to atraumatic needles in diagnostic lumbar punctures (LPs), providing Class I evidence in favor of the atraumatic needle.

Conclusions and Recommendations

• New Conclusion: Most studies in the anesthesiology literature, across several needle sizes, and now also one study providing Class I evidence in a patient population undergoing diagnostic LPs with a 22-gauge needle support the use of an atraumatic spinal needle to reduce the frequency of PLPHA (A*).

• Reaffirmation of a Previous Conclusion: Class I and Class II data in the anesthesiology and the neurology literature show that smaller needle size is associated with reduced frequency of PLPHA (A).

* Evidence rating key can be found on page 5 of this pocket guide.

This is a summary of the AAN and Child Neurology Society guideline on migraine headache. The guideline reviews the evidence on the pharmacological treatment of migraine in children and adolescents. Nonpharmacological treatments and biobehavioral measures are not addressed.

Recommendations

Acute Treatment of Migraine in Children and Adolescents

• Ibuprofen is effective and should be considered for the acute treatment of migraine in children (A*).

• Acetaminophen is probably effective and should be considered for the acute treatment of migraine in children (B).

• Sumatriptan nasal spray is effective and should be considered for the acute treatment of migraine in adolescents (A).

• There are no supporting data for the use of any oral “triptan” preparations in children or adolescents (U).

• There are inadequate data to make a judgment on the efficacy of subcutaneous sumatriptan (U).

Preventive Therapy of Migraine in Children and Adolescents

• Flunarizine is probably effective for preventive therapy and can be considered for this purpose, but it is not available in the United States (B).

• There is insufficient evidence to make any recommendations concerning the use of cyproheptadine, amitriptyline, divalproex sodium, topiramate, or levetiracetam (U).

• Recommendations cannot be made concerning propranolol or trazodone for preventive therapy, as the evidence is conflicting (U).

• Pizotifen, nimodipine, and clonidine did not show efficacy and are not recommended (B).

* Evidence rating key can be found on page 5 of this pocket guide.


This is a summary of the AAN and Child Neurology Society guideline on recurrent headache. The guideline concludes that recurrent headaches occur commonly in children and are diagnosed on a clinical basis rather than by testing. The routine use of diagnostic studies is not indicated when the clinical history has no associated risk factors and the child’s examination is normal.
Recommendations

Laboratory Studies and Lumbar Puncture

- There is inadequate documentation in the literature to support any recommendation as to the value of routine laboratory studies or performance of routine lumbar puncture (LP) in the evaluation of recurrent headache in children (U*).

EEG

- EEG is not recommended in the routine evaluation of a child with recurrent headaches, as it is unlikely to provide an etiology, improve diagnostic yield, or distinguish migraine from other types of headaches (C).
- Although the risk of future seizures is negligible in children with recurrent headache and paroxysmal EEG, future investigations for epilepsy should be determined by clinical follow-up (C).

Neuroimaging

- Obtaining a neuroimaging study on a routine basis is not indicated in children with recurrent headaches and a normal neurologic examination (B).
- Neuroimaging should be considered in children with an abnormal neurologic examination (e.g., focal findings, signs of increased intracranial pressure, significant alteration of consciousness), the coexistence of seizures, or both (B).
- Neuroimaging should be considered in children in whom there are historical features to suggest the recent onset of severe headache or change in the type of headache, or if there are associated features that suggest neurologic dysfunction (B).

* Evidence rating key can be found on page 5 of this pocket guide.


This is a summary of the AAN guideline on prevention of post-lumbar puncture headache (PLPHA). PLPHA has been defined in different ways. Definitions range from any headache (HA) after lumbar puncture (LP) to HA after LP with definite characteristics—in particular, a constant HA appearing or worsening significantly upon assuming the upright position and resolving or improving significantly upon lying down. Some of the definitions used do not permit excluding possible overlap between the PLPHA described and migraine without aura, at least in some of the patients. The authors elected to accept all definitions of PLPHA uncritically, but recommend that future studies of PLPHA adhere to rigorous definitions that will permit excluding other etiologies of HAs. Similarly, there is no uniform definition of “severe” PLPHA. Future studies should use established and well-defined criteria for PLPHA and its severity.
Recommendations

- Class I and Class II data in the anesthesiology literature and either Class I or Class II data in the neurology series show that smaller needle size is associated with reduced frequency of PLPHA \( (A^*) \). The actual choice of needle size will be influenced by balancing other considerations, such as ease of use, the need to measure pressures, and the flow rate, with the desire to prevent PLPHA.

- Class I data in the anesthesiology literature show that, when using a cutting needle, ensuring that the bevel direction is parallel to the dural fibers reduces the frequency of PLPHA \( (A) \).

- Class I data using a noncutting needle show that replacement of the stylet before the needle is withdrawn is associated with lower frequency of PLPHA \( (A) \).

- For spinal anesthesia, Class I data show that noncutting needles reduce the frequency of PLPHA \( (A) \). However, for diagnostic LPs, the data are inconclusive.

- Class I and Class II data have not demonstrated that the duration of recumbency following a diagnostic LP influences the occurrence of PLPHA.

- There is no evidence that the use of increased fluids prevents PLPHA.

* Evidence rating key can be found on page 5 of this pocket guide.
Guideline
This is a summary of the AAN guideline on the treatment of nervous system Lyme disease (Neurology 2007;69:91–102).

Tools & Resources
Please refer to www.aan.com to access the full guideline and the following companion tools:

- Clinician Summary
- Patient/Caregiver Summary
- Slide Presentation
- Clinical Example
- Poster

Treatment of Nervous System Lyme Disease (2007)
Endorsed by the Infectious Disease Society of America.

This guideline addresses the use of antibiotic treatment in patients with nervous system Lyme disease and post-Lyme syndrome. The recommendations address the needs of medical providers caring for patients with these conditions.

Recommendations

Treatment for Peripheral Nervous System Lyme Disease and Central Nervous Systems Lyme Disease

With or Without Parenchymal Involvement

- Parenteral ceftriaxone, cefotaxime, and penicillin are probably safe and effective (B*).

Without Parenchymal Involvement

- Oral doxycycline is probably safe and effective (B). Parenteral ceftriaxone, cefuroxime, and penicillin are probably safe and effective (B). Amoxicillin and cefuroxime axetil may provide alternatives, but supporting data are lacking.
- Although the evidence is stronger in adults than in children, all available evidence indicates that the responses to oral treatment are comparable in adults and children. It must be emphasized that no definitive data exist to establish the superiority, or lack thereof, of either oral or parenteral treatment. Specific regimens are listed in tables 1 and 2 below.
Table 1. Antimicrobial Regimens Used in Treatment of Nervous System Lyme Disease

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adult dose</th>
<th>Pediatric dose</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline* <em>(preferred)</em></td>
<td>100 (-200) mg BID</td>
<td>≥8 yo: 4 (-8) mg/kg/d in divided doses; max 200 mg/dose</td>
<td>B</td>
</tr>
<tr>
<td>Amoxicillin <em>(when doxycycline contraindicated)†</em></td>
<td>500 mg TID</td>
<td>50 mg/kg/d in 3 divided doses; max 500 mg/dose</td>
<td>C</td>
</tr>
<tr>
<td>Cefuroxime axetil <em>(when doxycycline contraindicated)†</em></td>
<td>500 mg BID</td>
<td>30 mg/kg/d in 2 divided doses; max 500 mg/dose</td>
<td>C</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2 g IV daily</td>
<td>50–75 mg/kg/d in 1 dose; max 2 g</td>
<td>B</td>
</tr>
<tr>
<td>Cefotaxime‡</td>
<td>2 g IV Q8H</td>
<td>150–200 mg/kg/d in 3–4 divided doses; max 6 g/day</td>
<td>B</td>
</tr>
<tr>
<td>Penicillin G‡</td>
<td>18–24 MU/d, divided doses Q4H</td>
<td>200–400,000 U/Kg/d divided Q4H; max 18–24 MU/day</td>
<td>B</td>
</tr>
</tbody>
</table>

For all, recommended duration is 14 days, although published studies have used courses ranging from 10 to 28 days without significantly different outcomes. *Tetracyclines are relatively contraindicated in children <8 years of age or in pregnant or lactating women. †These two oral regimens are effective in nonnervous system Lyme borreliosis. There are no data demonstrating efficacy in neuroborreliosis, but large numbers of patients have been treated with these regimens for other forms of Lyme disease without obvious subsequent onset of nervous system involvement. As such, they may be an oral alternative in individuals who cannot take doxycycline. ‡The antibiotic dosage should be reduced for patients with impaired renal function.

Table 2. Syndromes and Treatment Options

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>Parenteral, particularly if severe*</td>
</tr>
<tr>
<td>Any neurologic syndrome with cerebral spinal fluid (CSF) pleocytosis</td>
<td>Parenteral, particularly if severe*</td>
</tr>
<tr>
<td>Peripheral nerve radiculopathy, diffuse neuropathy, mononeuropathy multiplex, cranial neuropathy; normal CSF</td>
<td>Parenteral if treatment failure or if severe</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Posttreatment Lyme syndrome</td>
<td>No antibiotics indicated; symptomatic management only</td>
</tr>
</tbody>
</table>

*Available data in European neuroborreliosis indicate that oral doxycycline and parenteral ceftriaxone are equally effective in Lyme meningitis, and anecdotal data from the United States indicate that in patients with Lyme disease-associated facial palsy, response to oral treatment is sufficient so that CSF examination may be unnecessary. Although none of these studies is Class I, it was the consensus of the panel that, in the absence of brain or spinal cord involvement, oral treatment of neuroborreliosis is an acceptable option in appropriate circumstances. †Studies assessing oral treatment of neuroborreliosis have used only doxycycline. Other agents such as
amoxicillin or cefuroxime axetil may be effective in individuals who cannot tolerate doxycycline, but relevant data are lacking.

**Treatment of Post-Lyme Syndrome**

Prolonged courses of antibiotics do not improve outcome of post-Lyme syndrome, are potentially associated with adverse events, and are therefore not recommended (A).

* Evidence rating key can be found on page 5 of this pocket guide.
Guideline

This is a summary of the AAN and Child Neurology Society guideline on evaluation of the child with microcephaly (Neurology 2009;73:887–897).

Tools & Resources

Please refer to www.aan.com to access the full guideline and the following companion tools:

- Clinician Summary
- Patient/Caregiver Summary
- Clinical Example
- Poster
- Video
- Podcast

Summary

Microcephaly is an important neurologic sign, but there is nonuniformity in its definition and evaluation. Few data are available to inform recommendations regarding diagnostic testing of microcephaly. The yield of neuroimaging ranges from 43% to 80%. Genetic etiologies have been reported in 15.5% to 53.3%. The prevalence of metabolic disorders is unknown but is estimated to be 1%. Children with severe microcephaly (head circumference [HC] < –3 SD) are more likely (~80%) to have imaging abnormalities and more severe developmental impairments than those with milder microcephaly (–2 to –3 SD; ~40%). Coexistent conditions include epilepsy (~40%), cerebral palsy (~20%), mental retardation (~50%), and ophthalmologic disorders (~20% to ~50%).

Evaluation of the Child with Microcephaly (2009)

Recommendations

Neuroimaging

- Neuroimaging may be considered useful in identifying structural causes in the evaluation of the child with microcephaly (C*).
- 
  Clinical Context: MRI often reveals findings that are more difficult to visualize on CT, such as migrational disorders, callosal malformations, structural abnormalities in the posterior fossa, and disorders of myelination, and is considered the superior diagnostic test.

Genetic Testing

- Targeted genetic testing may be considered in the evaluation of the child with microcephaly in order to determine a specific etiology (C).
- 
  Clinical Context: Microcephaly has been associated with numerous genetic etiologies. Because the genetics of microcephaly is a rapidly evolving field, current data underestimate the importance and relevance of genetic testing.
as part of the diagnostic evaluation. Many of the microcephaly genes have been associated with specific phenotypes, allowing targeted clinical testing. However, insufficient data showing the diagnostic yield of these tests preclude specific recommendations for use.

**Metabolic Testing**

- There is insufficient evidence to support or refute obtaining metabolic testing on a routine basis for the evaluation of the newborn or infant with microcephaly (U).
- **Clinical Context:** Microcephaly is common in global developmental delay, and the yield of metabolic testing may be higher when the following are present: parental history of consanguinity, family history of similar symptoms in relatives, episodic symptoms, developmental regression, extracranial organ failure, or specific findings on neuroimaging. Metabolic testing may have a higher yield when microcephaly remains unexplained after other evaluations have been done.

**Epilepsy**

- Because children with microcephaly are at risk for epilepsy, physicians may consider educating caregivers of children with microcephaly on how to recognize clinical seizures (C).
- There are insufficient data to support or refute obtaining a routine EEG in a child with microcephaly (U).

**Cerebral Palsy**

- Because children with cerebral palsy (CP) are at risk for developing acquired microcephaly, serial HC measurements should be followed (A).
- Because children with microcephaly are at risk for CP, physicians and other care providers may consider monitoring them for early signs so that supportive treatments can be initiated (C).

**Mental Retardation**

- Because children with microcephaly are at risk for developmental disability, physicians should periodically assess development and academic achievement to determine whether further testing and rehabilitative efforts are warranted (A).

**Ophthalmological and Audiological Disorders**

- Screening for ophthalmological abnormalities in children with microcephaly may be considered (C).
- **Clinical Context:** Certain microcephaly syndromes are characterized by sensory impairments. Early identification of visual and hearing deficits may help identify a syndrome and the need for supportive care of the child.
Clinical Context

*Congenital Microcephaly*

- Many medical experts advocate doing a prompt, comprehensive evaluation of congenital microcephaly, given the risk of neurodevelopmental impairment and the parental anxiety associated with the diagnosis. Consulting a neurologist and geneticist can help to guide the diagnostic evaluation and support and educate families. Establishing a more specific diagnosis provides valuable information regarding etiology, prognosis, treatment, and recurrence risk. The initial history, examination, and screening laboratory testing may suggest a specific diagnosis or diagnostic category, allowing further screening or testing to be targeted. If the initial evaluation is negative and the child appears to have isolated microcephaly, a head MRI may help to categorize the type of microcephaly. Figure 12 presents an algorithm for evaluating congenital microcephaly.

Figure 12: Evaluation of congenital microcephaly

<table>
<thead>
<tr>
<th>Does newborn have clinical features, other organ involvement, vision/hearing impairments, or family history to suggest a specific disease or syndrome?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Do specific testing for that condition</td>
</tr>
<tr>
<td><strong>No</strong></td>
</tr>
<tr>
<td>Is the microcephaly proportionate with weight and height?</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Proportionate microcephaly. Does the child have neurologic signs or symptoms or a family history of childhood neurologic disease?</td>
</tr>
<tr>
<td><strong>No</strong></td>
</tr>
<tr>
<td>Obtain MRI for further evaluation</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>MRI shows a specific malformation or pattern of injury. Evaluate for that condition (appendix 3 of published guideline).</td>
</tr>
<tr>
<td><strong>No</strong></td>
</tr>
<tr>
<td>MRI is normal or nonspecific. Consider testing for infectious, toxic, genetic, or metabolic disorders (table 1 of published guideline).</td>
</tr>
<tr>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Observe and consider MRI, genetic, or metabolic testing if there are new neurologic signs or symptoms or worsening microcephaly.</td>
</tr>
</tbody>
</table>

Microcephaly
**Postnatal Onset Microcephaly [H3]**

- Microcephaly from acquired insults to the CNS or from progressive metabolic/genetic disorders is usually apparent by age 2 years. Mild or proportionate microcephaly may go unrecognized unless a child’s HC is measured accurately. Making comparisons to parents’ HCs may be important as familial forms of mild microcephaly have been described. Currently available assessment tools may not ultimately establish a specific etiologic diagnosis. Figure 13 presents an algorithm for evaluating postnatal onset microcephaly.

**Figure 13: Evaluation of postnatal onset microcephaly**

<table>
<thead>
<tr>
<th>Does child have clinical features, other organ involvement, vision/hearing impairments, or family history to suggest a specific disease or syndrome?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>No</strong></td>
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<tr>
<td><strong>Yes</strong></td>
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<tr>
<td><strong>No</strong></td>
</tr>
</tbody>
</table>

* Evidence rating key can be found on page 5 of this pocket guide.
**Guidelines**
The following pages summarize six AAN guidelines on multiple sclerosis (MS):

**Efficacy and Safety of Mitoxantrone (Novantrone) for Treating MS** *(Neurology 2010;74:1463–1470)*

**Use of Natalizumab (Tysabri) for Treating MS** *(Neurology 2008;71:766–773)*

**Neutralizing Antibodies to Interferon Beta** *(Neurology 2007;68:977–984; reaffirmed July 2010)*

**Use of Mitoxantrone (Novantrone) for Treating MS** *(Neurology 2003;61:1332–1338)*

**Utility of MRI in Suspected MS** *(Neurology 2003;61:602–611; reaffirmed October 2005 and November 2008)*

**Disease Modifying Therapies in MS** *(Neurology 2002;58:169–178; reaffirmed October 2003 and July 2008)*


**Tools & Resources**
Please refer to www.aan.com to access the full guidelines and the following companion tools:

- Clinician Summaries
- Patient/Caregiver Summaries
- Slide Presentations
- Posters
- Podcast
- Background/Data

**Efficacy and Safety of Mitoxantrone (Novantrone) for Treating MS** *(2010)*

See also “Use of Mitoxantrone (Novantrone) for Treating MS” *(2003)*.

This is a summary of the AAN guideline on mitoxantrone for treating multiple sclerosis (MS). The chemotherapeutic agent mitoxantrone (MX) was approved for use in MS in 2000. The original guideline (2003) concluded that MX probably reduced clinical attack rates, MRI activity, and disease progression. Subsequent reports of decreased systolic function, heart failure, and leukemia prompted the US Food and Drug Administration (FDA) to institute a “black box” warning in 2005. This review was undertaken to examine the available literature on the efficacy and safety of mitoxantrone use in patients with MS since the original guideline.
Conclusions

Efficacy

• No large-scale randomized controlled trial has replicated the Mitoxantrone in Multiple Sclerosis Group (MIMS) study since the original guideline. An MRI substudy of the MIMS trial did not show a benefit of MX on the primary endpoint (Class II evidence). A trial designed to assess the safety of MX induction before glatiramer acetate monotherapy demonstrated a greater reduction in contrast-enhancing lesions in patients treated with MX over 15 months, although no effect on relapses or Expanded Disability Status Scale progression was detected (Class I evidence). Therefore, the original recommendation remains Level B*.

Safety

• Cardiotoxicity: While the Class III and IV evidence available provides conflicting estimates of both the frequency and severity of MX-related cardiotoxicity, asymptomatic decreased systolic function occurs in approximately 12% of patients treated with MX, and congestive heart failure (CHF) occurs in approximately 0.4%.

• Leukemia: The literature on therapy-related acute leukemia (TRAL) in MX-treated patients with MS is also limited to Class III and IV evidence; however, the cumulative incidence appears to be ~0.8%. Both TRAL and systolic dysfunction can occur at any time after initiation of MX, including early in the treatment course.

• Recommendations on MX use reflecting the potential for harm would require a risk-benefit analysis and are beyond the scope of an evidence-based guideline. In the absence of such an analysis, it is reasonable for clinicians to follow the recommendations outlined in the product monograph and include ejection fraction assessments before initiating treatment and administering each dose of MX and yearly after discontinuation of treatment. It is not known whether patients treated with MX with asymptomatic decreased left ventricular ejection fraction (LVEF) will experience long-term sequelae. The long-term sequelae of asymptomatic cardiotoxicity are not clear. It is reasonable for clinicians to monitor patients for TRAL after MX therapy with periodic complete blood cell counts, although the optimal timing of such monitoring is not known.

• Clinicians contemplating MX administration for an individual patient with MS must weigh the potential for benefit against the potential for harm given the ~12% risk of systolic dysfunction and ~0.8% risk of TRAL and the availability of alternative therapies with less severe toxicities (e.g., interferon-β and glatiramer acetate) for patients with relapsing-remitting multiple sclerosis (RRMS).

* Evidence rating key can be found on page 5 of this pocket guide.
Use of Natalizumab (Tysabri) for Treating MS (2008)

This is a summary of the AAN guideline on the clinical and radiologic impact of natalizumab (Tysabri) for treating multiple sclerosis (MS).

Recommendations

- Strong evidence suggests that natalizumab reduces measures of disease activity such as clinical relapse rate, Gd-enhancement, and new and enlarging T2 lesions in patients with relapsing multiple sclerosis (MS) (A*).
- Strong evidence suggests that natalizumab improves measures of disease severity such as the Expanded Disability Status Scale (EDSS) progression rate and the T2-hyperintense and T1-hypointense lesion burden seen on MRI in patients with relapsing MS (A).
- Because of the possibility that natalizumab therapy may be responsible for the increased risk of progressive multifocal leukoencephalopathy (PML), it is recommended that natalizumab be reserved for use in selected patients with relapsing remitting disease who have failed other therapies either through continued disease activity or medication intolerance, or who have a particularly aggressive initial disease course.
- There is insufficient evidence to support the relative efficacy of natalizumab compared to other available disease-modifying therapies (U).
- There is insufficient evidence to support the value of natalizumab in the treatment of secondary progressive multiple sclerosis (SPMS) (U).
- Good evidence supports the value of adding natalizumab to patients already receiving IFNβ-1a (interferon beta 1-a), 30 μg, intramuscular once weekly (B).
- There is insufficient evidence regarding the value either of adding IFNβ therapy to the care of patients already receiving natalizumab to treat relapsing-remitting multiple sclerosis (RRMS) or of continuing IFNβ therapy once natalizumab therapy is started (U).
- Strong evidence suggests that there is an increased risk of developing PML in natalizumab-treated patients for combination therapy (A).
- Weak evidence suggests that there is an increased risk of developing PML in natalizumab-treated patients for monotherapy (C).
- Weak evidence suggests that there may be an increased risk of other opportunistic infections in natalizumab-treated patients (C).
- Because it may increase the risk of PML, combination therapy with IFNβ and natalizumab should not be used. There are also no data to support the use of natalizumab combined with other disease-modifying agents as compared to natalizumab alone. The use of natalizumab in combination with agents not inducing immune suppression should be reserved for properly controlled and monitored clinical trials.
Since the development of this guideline, additional cases of PML have been reported in patients receiving natalizumab monotherapy. This observation indicates that natalizumab, by itself, is a risk factor for PML. However, the evidence has not been formally reviewed by the AAN’s Therapeutics and Technology Assessment Subcommittee.

* Evidence rating key can be found on page 5 of this pocket guide.

**Neutralizing Antibodies to Interferon Beta** (2007; reaffirmed 2010)

This is a summary of the AAN guideline on neutralizing antibodies (NAbs) to interferon beta (IFNβ) in the treatment of multiple sclerosis (MS). The development of NAbs to proteins administered therapeutically is often associated with a reduction in the biologic actions that these proteins exert. It is therefore surprising that the clinical and radiographic impact of NAbs to IFNβ in the treatment of MS is controversial. This assessment evaluates the clinical and radiographic impact of NAbs in this setting and considers some of the difficulties in this research area that may explain the ongoing controversy. Thus, a brief overview of IFN biology is provided in the supplementary material to this assessment (available at www.neurology.org).

**Conclusions**

- Treatment of MS with IFNβ (IFNβ-1a for intramuscular injection, IFNβ-1a for subcutaneous injection multiple times per week, and IFNβ-1b) is associated with the production of NAbs to the IFNβ molecule (A*).
- It is probable that the presence of NAbs, especially in persistently high-titers, is associated with a reduction in the radiographic and clinical effectiveness of IFNβ treatment (B).
- It is probable that the rate of NAb production is less with IFNβ-1a treatment compared to IFNβ-1b treatment (B). However, because of the variability of the prevalence data, and because NAbs disappear in the majority of patients even with continued treatment (especially in those with low-titer NAbs), the magnitude and persistence of any difference in seroprevalence between these forms of IFNβ is difficult to determine.
- It is probable that the seroprevalence of NAbs to IFNβ is affected by one or more of the following: its formulation, dose, route of administration, or frequency of administration (B). Regardless of the explanation, it seems clear that IFNβ-1a (as it is currently formulated for intramuscular injection) is less immunogenic than the current IFNβ preparations (either IFNβ-1a or IFNβ-1b) given multiple times per week subcutaneously (A). Because NAbs may disappear in many patients with continued therapy, the persistence of this difference is difficult to determine (B).
- Although the finding of sustained high-titer NAbs (> 100-200 NU/mL) has been associated with a reduction in the therapeutic effects of IFNβ on radiographic and clinical measures of MS disease activity, there is
insufficient information on the utilization of NAb testing to provide specific recommendations regarding when to test, which test to use, how many tests are necessary, and which cutoff titer to apply (U).

**Recommendations**

- Due to a paucity of evidence, it is impossible to make recommendations on this controversial issue.

* Evidence rating key can be found on page 5 of this pocket guide.

**Use of Mitoxantrone (Novantrone) for Treating MS** (2003)

* See also “Efficacy and Safety of Mitoxantrone (Novantrone) for Treating MS” (2010).

This is a summary of the AAN guideline on use of mitoxantrone for treating multiple sclerosis (MS). Mitoxantrone is the first drug approved for the treatment of secondary progressive multiple sclerosis (SPMS) in the United States.

**Recommendations**

- On the basis of evidence from a single Class I study and a few Class II or III studies, it appears that mitoxantrone may have a beneficial effect on disease progression in patients with MS whose clinical condition is deteriorating (B*). In general, however, this agent is of limited use and of potentially great toxicity. Therefore, it should be reserved for patients with rapidly advancing disease who have failed other therapies.

- On the basis of several consistent Class II and III studies, mitoxantrone probably reduces the clinical attack rate and reduces attack-related MRI outcomes in patients with relapsing MS (B). The potential toxicity of mitoxantrone, however, considerably limits its use in patients with relapsing forms of MS.

- Because of the potential toxicity of mitoxantrone, it should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapeutic agents (A). In addition, patients being treated with mitoxantrone should be monitored routinely for cardiac, liver, and kidney function abnormalities (A).

* Evidence rating key can be found on page 5 of this pocket guide.

**Utility of MRI in Suspected MS** (2003; reaffirmed 2005 and 2008)

This is a summary of the AAN guideline on utility of MRI in suspected multiple sclerosis (MS). Advancements in imaging technologies and newly evolving treatments offer the promise of more effective management strategies for MS. Until recently, confirmation of the diagnosis of MS has generally required the demonstration of clinical activity that is disseminated in both time and space.
Nevertheless, with the advent of MRI techniques, occult disease activity can be demonstrated in 50% to 80% of patients at the time of the first clinical presentation. Prospective studies have shown that the presence of such lesions predicts future conversion to clinically definite (CD) MS.

**Recommendations**

- On the basis of consistent Class I, II, and III evidence, in clinically isolated demyelinating (CIS) patients, the finding of 3 or more white matter lesions on a T2-weighted MRI scan is a very sensitive predictor (>80%) of the subsequent development of CDMS within the next 7 to 10 years if other diagnoses are ruled out (A*). It is possible that the presence of even a smaller number of white matter lesions (e.g., 1 to 3) may be equally predictive of future MS although this relationship requires better clarification. Periventricular lesions increase the likelihood of CDMS on follow-up.

- The appearance of new T2 lesions or new Gd-enhancement 3 or more months after a clinically isolated demyelinating episode (and after a baseline MRI assessment) is highly predictive of the subsequent development of CDMS in the near term (A).

- The probability of making a diagnosis other than MS in CIS patients with any of the above MRI abnormalities is quite low, once alternative diagnoses that can mimic MS or the radiographic findings of MS have been excluded (A). (See figure 14.)

- The presence of 2 or more Gd-enhancing lesions at baseline is highly predictive of the future development of CDMS (B).

- The MRI features helpful in the diagnosis of primary progressive multiple sclerosis (PPMS) cannot be determined from the existing evidence (U).

**Figure 14. Diagnostic considerations in patients with suspected MS and/or MRI white matter abnormalities**

- Acute disseminated encephalomyelitis
- Age-related white matter changes
- Bacterial infections (syphilis, Lyme disease)
- Behcet’s disease
- Cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy (CADASIL)
- Cervical spondylosis or stenosis
- HIV infection
- Human T-lymphotrophic virus I/II
- Ischemic optic neuropathy (arteritic and nonarteritic)
- Leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
- Migraine
- Neoplasms (e.g., lymphoma, glioma, meningioma)
- Sarcoid
Disease Modifying Therapies in MS (2002; reaffirmed 2003 and 2008)

This is a summary of the AAN guideline on disease modifying therapies in multiple sclerosis (MS). The purpose of this assessment is to consider the clinical utility of these disease-modifying agents, including the antiinflammatory, immunomodulatory, and immunosuppressive treatments that are currently available. Symptomatic and reparative therapies will not be considered.

**Recommendations**

**Glucocorticoids**

- Glucocorticoid treatment has been demonstrated to have a short-term benefit on the speed of functional recovery in patients with acute attacks of MS. It is appropriate, therefore, to consider for treatment with glucocorticoids any patient with an acute attack of MS (A*).

- There does not appear, however, to be any long-term functional benefit after the brief use of glucocorticoids in this clinical setting (B).

- Currently, there is no compelling evidence to indicate that these clinical benefits are influenced by the route of glucocorticoid administration, the particular glucocorticoid prescribed, or the dosage of glucocorticoid, at least at the doses that have been studied to date (C).

- It is considered possible that regular-pulse glucocorticoids may be useful in the long-term management of patients with relapsing-remitting multiple sclerosis (RRMS) (C).

**Interferon Beta**

- Interferon beta (IFNβ) has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with MS or with clinically isolated syndromes who are at high risk for developing MS (A). Treatment of MS with IFNβ produces a beneficial effect on MRI measures of disease severity such as T2 disease burden and probably also slows sustained disability progression (B).

- As a result, it is appropriate to consider IFNβ for treatment in any patient who is at high risk for developing clinically definite multiple sclerosis.
(CDMS), or who already has either RRMS or secondary progressive multiple sclerosis (SPMS) and is still experiencing relapses (A). The effectiveness of IFNβ in patients with SPMS but without relapses is uncertain (U).

- It is possible that certain populations of MS patients (e.g., those with more attacks or at earlier disease stages) may be better candidates for therapy than others, although, at the moment, there is insufficient evidence regarding these issues (U).

- It is considered probable that there is a dose-response curve associated with the use of IFNβ for the treatment of MS (B). It is possible, however, that a portion of this apparent dose-effect instead may be due to differences in the frequency of IFNβ administration (rather than dose) between studies.

- The route of administration of IFNβ is probably not of clinical importance, at least with regard to efficacy (B). The side-effect profile, however, does differ between routes of administration. There is no known clinical difference between the different types of IFNβ, although this has not been thoroughly studied (U).

- Treatment of patients with MS with IFNβ is associated with the production of neutralizing antibodies (NAb) (A). The rate of NAb production, however, is probably less with IFNβ-1a treatment than with IFNβ-1b treatment (B). The biologic effect of NAb is uncertain, although their presence may be associated with a reduction in clinical effectiveness of IFNβ treatment (C). Whether there is a difference in immunogenicity between subcutaneous and intramuscular routes of administration is unknown (U). The clinical utility of measuring NAb in an individual on IFNβ therapy is uncertain (U).

**Glatiramer Acetate**

- Glatiramer acetate has been demonstrated to reduce the attack rate (whether measured clinically or by MRI) in patients with RRMS (A). Treatment with glatiramer acetate produces a beneficial effect on MRI measures of disease severity such as T2 disease burden, and possibly also slows sustained disability progression in patients with RRMS (C).

- As a result, it is appropriate to consider glatiramer acetate for treatment in any patient who has RRMS (A). Although it may be that glatiramer acetate also is helpful in patients with progressive disease, there is no convincing evidence to support this hypothesis (U).

**Cyclophosphamide**

- Pulse cyclophosphamide treatment does not seem to alter the course of progressive MS (B).

- It is possible that younger patients with progressive MS might derive some benefit from pulse plus booster cyclophosphamide treatment (U).

**Methotrexate**

- It is considered possible that methotrexate favorably alters the disease course in patients with progressive MS (C).
Azathioprine

- It is considered possible that azathioprine reduces the relapse rate in patients with MS (C).
- Its effect on disability progression has not been demonstrated (U).

Cladribine

- It is concluded that cladribine reduces Gd enhancement in patients with both relapsing and progressive forms of MS (A).
- Cladribine treatment does not, however, appear to alter favorably the course of the disease, either in terms of attack rate or disease progression (C).

Cyclosporine

- It is considered possible that cyclosporine provides some therapeutic benefit in progressive MS (C).
- However, the frequent occurrence of adverse reactions to treatment, especially nephrotoxicity, together with the small magnitude of the potential benefit, makes the risk/benefit of this therapeutic approach unacceptable (B).

Mitoxantrone

- It is concluded that mitoxantrone probably reduces the attack rate in patients with relapsing forms of MS (B). The potential toxicity of mitoxantrone, however, may outweigh the clinical benefits early in the course of the disease.
- It is considered possible that mitoxantrone has a beneficial effect on disease progression in MS, although, at the moment, this clinical benefit has not been established (C). (Note: This recommendation has been updated to a Level B recommendation due to a Class I study [Neurology 2003;61:1332–1338]).

Intravenous Immunoglobulin

- The studies of intravenous immunoglobulin (IVIg) to date have generally involved small numbers of patients, have lacked complete data on clinical and MRI outcomes, or have used methods that have been questioned. It is, therefore, only possible that IVIg reduces the attack rate in RRMS (C).
- The current evidence suggests that IVIg is of little benefit with regard to slowing disease progression (C).

Plasma Exchange

- Plasma exchange (PE) is of little or no value in the treatment of progressive MS (A).
- It is considered possible that PE may be helpful in the treatment of severe acute episodes of demyelination in previously nondisabled individuals (C).

Sulfasalazine

- It is concluded that treatment of MS with sulfasalazine provides no therapeutic benefit in MS (B).

* Evidence rating key can be found on page 5 of this pocket guide.

This is a summary of the AAN guideline on utility of evoked potentials (EPs) in patients with suspected multiple sclerosis (MS). The diagnosis of MS remains primarily clinical, requiring evidence of white matter lesions disseminated in space and time. Some patients with suspected MS not fulfilling clinical dissemination criteria (MS suspects) have abnormal EPs that identify clinically unsuspected lesions. Current diagnostic criteria allow MS suspects to be reclassified into definite MS categories if EPs identify clinically silent lesions.

Recommendations

If you are considering EPs in patients with suspected MS for the purpose of finding clinically silent lesions:

- Visual evoked potentials (VEPs) are recommended as probably useful to identify patients at increased risk for developing clinically definite multiple sclerosis (CDMS) (B*).
- Somatosensory evoked potentials (SEPs) are recommended as possibly useful to identify patients at increased risk for developing CDMS (C).
- Evidence is insufficient at this time to recommend brainstem auditory evoked potentials (BAEPs) as a useful test to identify patients at increased risk for developing CDMS (B).

* Evidence rating key can be found on page 5 of this pocket guide.
Guideline

This is a summary of the AAN guideline on symptomatic treatment of muscle cramps (Neurology 2010;74:691–696).

Tools & Resources

Please refer to www.aan.com to access the full guideline and the following companion tools:

- Clinician Summary
- Patient/Caregiver Summary
- Poster
- Podcast

Endorsed by the American Association of Neuromuscular and Electrodiagnostic Medicine.

Summary

A US Food and Drug Administration (FDA) advisory in 2006 warned against the off-label use of quinine sulfate and its derivatives in the treatment of muscle cramps. Physicians are faced with a difficult scenario in choosing a treatment regimen for patients with muscle cramps. This guideline systematically reviews the available evidence on the symptomatic treatment of muscle cramps.

There are Class I studies showing the efficacy of quinine derivatives for treatment of muscle cramps. However, the benefit is modest, and there are adverse effects from published prospective trials as well as case reports. There is one Class II study each to support the use of naftidrofuryl, vitamin B complex, lidocaine, and diltiazem in the treatment of muscle cramps.

Symptomatic Treatment for Muscle Cramps (2010)

Recommendations

Nonpharmacologic Treatments

Data are insufficient to support or refute the efficacy of calf stretching in reducing the frequency of muscle cramps (U*).

Pharmacologic Treatments

- Although likely effective (A), the use of quinine derivatives for treatment of cramps should be avoided for routine treatment of cramps. These agents should only be considered when cramps are very disabling, no other agents relieve symptoms, and there is careful monitoring of side effects. They should only be used after informing the patient of the potentially serious side effects.
- Naftidrofuryl, diltiazem, and vitamin B complex may be considered for the treatment of muscle cramps (C).

* Evidence rating key can be found on page 5 of this pocket guide.
Guidelines
The following pages summarize two AAN guidelines on myasthenia:

Tools & Resources
Please refer to [www.aan.com](http://www.aan.com) to access the full guidelines and the following companion tools:
- Poster
- Background/Data

Medical Treatment of Ocular Myasthenia
(2007; reaffirmed 2010)
This is a summary of the AAN guideline on ocular myasthenia gravis (MG). This guideline aims to determine what pharmacologic treatments lead to improvement in ocular symptoms (diplopia and ptosis) and what pharmacologic treatments are associated with a reduced risk of progression from ocular to generalized MG.

**Recommendations**

**Immunosuppressive Agents**
- There is insufficient evidence to support or refute the efficacy of cholinesterase inhibitors, corticosteroids, or other immunosuppressive agents with respect to improvement of ocular symptoms and ocular myasthenia (**U**).

**Cholinesterase Inhibitors**
- There is insufficient evidence to support or refute the use of cholinesterase inhibitors to reduce the risk of progression from ocular to generalized MG (**U**).
- On the basis of data from several observational studies, there is insufficient evidence to support or refute the use of corticosteroids and azathioprine to reduce the risk of progression from ocular to generalized MG (**U**).

* Evidence rating key can be found on page 5 of this pocket guide.

This is a summary of the AAN guideline on thymectomy for autoimmune myasthenia gravis (MG). This guideline systematically reviewed the controlled but nonrandomized studies describing outcomes in MG patients undergoing and not undergoing thymectomy.

Conclusions

- Positive associations in most studies between thymectomy and MG remission and improvement (median relative rate of medication-free remission, 2.1; asymptomatic, 1.6; improvement, 1.7)
- Confounding differences in baseline characteristics of prognostic importance between thymectomy and nonthymectomy patient groups in all studies
- Persistent positive associations between thymectomy and improved MG outcomes after controlling for single confounding variables such as age, gender, and severity of MG
- Conflicting associations between thymectomy and improved MG outcomes in studies controlling for multiple confounding variables simultaneously
- The authors could not determine from the available studies whether the observed association between thymectomy and improved MG outcome was a result of a thymectomy benefit or was merely a result of the multiple differences in baseline characteristics between the surgical and nonsurgical groups. On the basis of these findings, the authors conclude that the benefit of thymectomy in nonthymomatous autoimmune MG has not been established conclusively.

Recommendation

- For patients with nonthymomatous autoimmune MG, thymectomy is recommended as an option to increase the probability of remission or improvement (C*).

* Evidence rating key can be found on page 5 of this pocket guide.
The following pages summarize two AAN, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation guidelines on neuropathy and pain; one AAN and European Federation of Neurological Societies guideline on pain; and five AAN guidelines on neuropathy and pain:

Guidelines


Diagnostic Evaluation and Treatment of Trigeminal Neuralgia (Neurology 2008;71:1183–1190)

Botulinum Neurotoxin in the Treatment of Autonomic Disorders and Pain (Neurology 2008;70:1707–1714)

Use of Epidural Steroid Injections to Treat Radicular Lumbosacral Pain (Neurology 2007;68:723–729; reaffirmed July 2010)


Tools & Resources

Please refer to www.aan.com to access the full guidelines and the following companion tools:

• Clinician Summaries
• Patient/Caregiver Summaries
• Slide Presentations
• Clinical Examples
• Posters
• Podcasts
Efficacy of TENS for Treating Pain in Neurologic Disorders (2010)

This is a summary of the AAN guideline on the efficacy of transcutaneous electric nerve stimulation (TENS) in the treatment of pain, specifically the pain associated with neurologic disorders. TENS has been used in the treatment of neurologic disorders for the last several decades. The biologic basis of the analgesic effect of TENS is not known, but the rationale for the use of TENS is based on the gate theory of pain. A fundamental question in any therapeutic trial is whether adequate blinding can be maintained for the intervention. In a study of TENS-naïve participants with chronic low back pain, TENS was compared to sham TENS (TENS-sham; in this case a nonfunctioning unit identical to the TENS unit with a light flashing at the stimulus frequency indicating that the unit was “on”). The blinding was mostly successful, with 100% of the TENS group and 84% of the TENS-sham group identifying their unit as working, though with a lesser degree of conviction in the TENS-sham group.

Recommendations

Chronic Low Back Pain

- TENS is not recommended for the treatment of chronic low back pain due to lack of proven efficacy (A*).

Painful Diabetic Neuropathy

- TENS should be considered for the treatment of painful diabetic neuropathy (B).
- Clinical Context: Many treatment options are commonly used for diabetic neuropathy, but there are presently no comparative studies of TENS to other treatment options.

* Evidence rating key can be found on page 5 of this pocket guide.

Distal Symmetric Polyneuropathy: Laboratory and Genetic Testing (2009)

This is a summary of the AAN, American Association of Neuromuscular and Electrodagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation guideline on laboratory and genetic testing in the evaluation of distal symmetric polyneuropathy (DSP). DSP is the most common variety of neuropathy. Since the evaluation of this disorder is not standardized, the available literature was reviewed to provide evidence-based guidelines regarding the role of laboratory and genetic tests for the assessment of DSP. The diagnosis of DSP should be based upon a combination of clinical symptoms, signs, and electrodiagnostic criteria.
Recommendations

Screening Laboratory Testing

• Screening laboratory tests may be considered for all patients with DSP (C*).
• Although routine screening with a panel of basic tests is often performed, those tests with the highest yield of abnormality are blood glucose, serum B12 with metabolites (methylmalonic acid with or without homocysteine), and serum protein immunofixation electrophoresis (C).
• When routine blood glucose testing is not clearly abnormal, other tests for prediabetes (impaired glucose tolerance) such as a glucose tolerance test (GTT) may be considered in patients with DSP, especially if it is accompanied by pain (C).
• Although there are no control studies (U) regarding when to recommend the use of other specific laboratory tests, clinical judgment correlated with the clinical picture will determine which additional laboratory investigations are necessary.

Genetic Testing

• Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies (A).
• Genetic testing may be considered in patients with a cryptogenic polyneuropathy and classic hereditary neuropathy phenotype (C). (See figure 15.)
• There is insufficient evidence to support or refute the usefulness of routine genetic testing in cryptogenic polyneuropathy patients without a classic hereditary phenotype (U).

Clinical Context

• To achieve the highest yield, the genetic testing profile should be guided by the clinical phenotype, inheritance pattern (if available), and electrodiagnostic (EDX) features (demyelinating versus axonal).
Figure 15: Evaluation of suspected hereditary neuropathies

Positive family history

EMG/NCS

Demyelinating

1st tier

AD

PMP22 dup 70%

MPZ mut 5%
PMP22 mut 2.5%

2nd tier

AD

GJB1 12%

MFN2 mut 33%

3rd tier

AR

X

PRX mut

GDAP1 mut

RAB7 mut

GARS mut

NEFL mut

GDAP1 mut

Axonal

Negative family history

EMG/NCS

Index of suspicion for CMT high

30% of mutations are de novo, molecular testing

Demyelinating

1st tier

PMP22 dup

GJB1 mut

MFN2 mut

GJB1 mut

2nd tier

MPZ mut 5%
PMP22 mut 2.5%

1st tier

AD

AR

X

3rd tier

GJB1 12%

MPZ mut 5%

EGR2 mut

LITAF mut

PRX mut

GDAP1 mut

RAB7 mut

GARS mut

NEFL mut

GDAP1 mut

*Evidence rating key can be found on page 5 of this pocket guide.

This is a summary of the AAN, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation guideline on autonomic testing, nerve biopsy, and skin biopsy in the evaluation of distal symmetric polyneuropathy (DSP). DSP is the most common variety of neuropathy. Since the evaluation of this disorder is not standardized, the available literature was reviewed to provide evidence-based guidelines regarding the role of autonomic testing, nerve biopsy, and skin biopsy for the assessment of polyneuropathy. The diagnosis of DSP should be based upon a combination of clinical symptoms, signs, and electrodiagnostic criteria.

Recommendations

Autonomic Testing

- Autonomic testing should be considered in the evaluation of patients with polyneuropathy to document autonomic nervous system involvement (B*).
- Autonomic testing should be considered in the evaluation of patients with suspected autonomic neuropathies (B).
- Autonomic testing may be considered in the evaluation of patients with suspected distal small fiber sensory polyneuropathy (SFSN) (C).

Composite Autonomic Scoring Scale

- The combination of autonomic screening tests in the Composite Autonomic Scoring Scale (CASS) should be considered to achieve the highest diagnostic accuracy (B).

Nerve Biopsy

- No recommendations can be made regarding the role of nerve biopsy in determining the etiology of DSP (U).

Skin Biopsy

- For symptomatic patients with suspected polyneuropathy, skin biopsy may be considered to diagnose the presence of a polyneuropathy, particularly SFSN (C).

* Evidence rating key can be found on page 5 of this pocket guide.

Diagnostic Evaluation and Treatment of Trigeminal Neuralgia (2008)

This is a summary of the AAN and European Federation of Neurological Societies guideline on the diagnostic evaluation and treatment of patients with trigeminal neuralgia (TN). The annual incidence of TN is 4 to 5 in 100,000. The latest classification of the International Headache Society distinguishes between classic and symptomatic TN. Classic TN (CTN) includes all cases without an established etiology. The diagnosis of CTN also
requires that there be no clinically evident neurologic deficit. The diagnosis of symptomatic TN (STN) is made when investigations identify a structural abnormality other than potential vascular compression affecting the trigeminal nerve. Such abnormalities include multiple sclerosis (MS) plaques, tumors, and abnormalities of the skull base.

**Recommendations**

**Diagnostic**

**Routine Neuroimaging**

- Weak evidence indicates that for patients with TN, routine imaging may be considered to identify a cause in up to 15% of patients with STN (C*).
- Clinical Context: The initial diagnostic evaluation of a patient with TN naturally focuses on those clinical characteristics known to identify patients with STN. Those characteristics include the presence of trigeminal sensory deficits and bilateral involvement.

**Clinical or Laboratory Features**

- Good evidence indicates that measuring trigeminal reflexes in a qualified electrophysiological laboratory should be considered useful for distinguishing STN from CTN (B).
- Clinical Context: If after the initial evaluation the clinician remains suspicious of STN, further testing is desirable. On the basis of cost, local expertise and availability, and patient preferences, obtaining trigeminal reflex testing or head imaging are both reasonable next steps.

**High-resolution MRI**

- There is insufficient evidence to support or refute the usefulness of MRI to identify vascular contact in CTN or to indicate the most reliable MRI technique (U).
- Clinical Context: Because of a high diagnostic accuracy, MRI might reasonably be foregone in a patient with normal trigeminal reflexes.

**Pharmacologic Treatment**

**CTN Pain Treatment**

- Strong evidence supports that carbamazepine (CBZ) should be offered to treat CTN pain (A).
- Good evidence supports that oxcarbazepine (OXC) should be considered to treat CTN pain (B).
- Clinical Context: The two drugs to consider as first-line therapy in TN are CBZ (200–1,200 mg/day) and OXC (600–1,800 mg/day). Although the evidence for CBZ is stronger than for OXC, the latter may pose fewer safety concerns.
- Weak evidence supports that baclofen, lamotrigine (LTG), and pimozide may be considered to treat CTN pain (C).
Good evidence supports that topical ophthalmic anesthesia should not be considered to treat CTN pain (B).

Clinical Context: There is little evidence to guide the clinician on the treatment of TN patients that who fail first-line therapy. Some evidence supports add-on therapy with LTG or a switch to baclofen (pimozide being no longer in use).

**STN Pain Treatment**

- There is insufficient evidence to support or refute the effectiveness of any medication in treating pain in STN (U).
- The effect of other drugs commonly used in neuropathic pain is unknown. There are no published studies directly comparing polytherapy with monotherapy.

**Intravenous Drug Treatment**

- There is insufficient evidence to support or refute the efficacy of intravenous medications for the treatment of pain from TN (U).

**Surgical Treatment**

- There is insufficient evidence to allow conclusions as to when surgery should be offered (U).
- Clinical Context: Referral for a surgical consultation seems reasonable in TN patients refractory to medical therapy. Some TN experts believe TN patients failing to respond to first-line therapy are unlikely to respond to alternative medications and suggest early surgical referral.
- There is weak evidence to support that early surgical therapy may be considered for patients with TN-refractory medical therapy (C).
- There is weak evidence to support percutaneous procedures on the Gasserian ganglion, gamma knife, and microvascular decompression (C).
- There is insufficient evidence to support or refute the effectiveness of the surgical management of TN in patients with MS (U).

* Evidence rating key can be found on page 5 of this pocket guide.

**Botulinum Neurotoxin in the Treatment of Autonomic Disorders and Pain (2008)**

*Endorsed by the American Academy of Physical Medicine and Rehabilitation and the American Association of Neuromuscular and Electrodiagnostic Medicine.*

This is a summary of the AAN guideline on botulinum neurotoxin (BoNT) in the treatment of autonomic disorders and pain. An increasing number of studies, including placebo-controlled trials, demonstrate that BoNT may be a valuable agent to treat autonomic disorders associated with localized cholinergic overactivity. Its mode of action in pain, however, is less well understood.
Recommendations

Axillary Hyperhidrosis
• BoNT should be offered as a treatment option (A*).

Palmar Hyperhidrosis and Drooling
• BoNT should be considered as a treatment option (B).
  
  *Clinical Context:* Many physicians offer BoNT to these patients who are unresponsive to topical treatment as an alternative to iontophoresis or sympathectomy.

Gustatory Sweating
• BoNT may be considered as a treatment option (C).
  
  *Clinical Context:* The evidence for BoNT in gustatory sweating is suboptimal. There are not effective alternative treatments.

Neurogenic Detrusor Overactivity
• BoNT should be offered as a treatment option (A).

Detrusor Sphincter Dyssynergia
• BoNT should be considered for detrusor sphincter dyssynergia (DSD) in patients with spinal cord injury (B).
  
  *Clinical Context:* There are limited head-to-head comparisons of treatment options in DSD.

Low-back Pain
• BoNT may be considered as a treatment option of patients with chronic predominantly unilateral low-back pain (LBP) (C).
  
  *Clinical Context:* Evaluation and treatment of LBP is complicated by its diverse potential causes. In most clinical settings, it is difficult to diagnose the precise origin of pain and therefore creates challenges in study design, particularly in the selection of homogeneous subject populations.

Chronic Daily Headache
• There is insufficient evidence to support or refute a benefit of BoNT for the treatment of chronic daily headache (U).

Chronic Tension-type Headache
• BoNT injections should not be considered (B).

Episodic Migraine
• BoNT injections should not be considered (B).
  
  *Clinical Context:* It is possible that underdosing and suboptimal muscle selection may account for some of the reported failures in studies of BoNT in headache.

* Evidence rating key can be found on page 5 of this pocket guide.
Use of Epidural Steroid Injections to Treat Radicular Lumbosacral Pain (2007; reaffirmed 2010)

This is a summary of the AAN guideline on use of epidural steroid injections to treat radicular lumbosacral pain. The guideline aims to determine if the treatment is effective when used to relieve sciatic pain and to postpone or avoid surgery. The guideline concludes that epidural steroid injections may result in some improvement in radicular lumbosacral pain when assessed between 2 and 6 weeks following the injection and that, in general, the injections for pain do not affect average impairment of function or the need for surgery, nor do they provide long-term pain relief beyond 3 months. There is insufficient evidence to make any recommendation for the use of epidural steroid injections to treat radicular cervical pain.

Recommendations

- Epidural steroid injections may result in some improvement in radicular lumbosacral pain when determined between 2 and 6 weeks following the injection, as compared to control treatment (C*). The average magnitude of effect is small, and the generalizability of the observation is limited by the small number of studies, limited to highly selected patient populations, the few techniques and doses studied, and variable comparison treatments.

- In general, epidural steroid injections for radicular lumbosacral pain have shown no impact on average impairment of function, on need for surgery, or on long-term pain relief beyond 3 months. Their routine use for these indications is not recommended (B).

- Data on use of epidural steroid injections to treat cervical radicular pain are inadequate to make any recommendation (U).

Principal Findings in Clinical Perspective

Amelioration of Pain

- The findings of four high-quality studies are internally consistent, showing the following efficacy pattern compared to a control group: no efficacy at 24 hours, some efficacy at 2 to 6 weeks, no difference or rebound worsening at 3 and 6 months, and no difference at 1 year.

- These results support the individual perception of benefit of epidural steroids, expressed in terms of short-term symptomatic relief, a positive result in and of itself.

- However, the average effect difference (advantage of steroids over control treatment) was small, usually falling short of the value proposed as a clinically meaningful average difference—15 mm on the 100 mm visual analogue pain scale.

Avoidance of Surgery

- The data on face value are conflicting, with the better designed studies
showing no benefit to epidural steroids.

- The data do not permit inferring if surgery is avoided due to the treatment effect of injected steroids, due to placebo effect, or because the treatment “buys time” for a natural history of improvement.

- The data do not address how epidural steroid injections might compare to other treatment modalities and the role of patient and provider characteristics, including temperament and pain tolerance, in selecting among various treatment options.

- The recommendations gave greater weight to the data from the better designed studies, showing that epidural steroid injections did not result in less surgery.

* Evidence rating key can be found on page 5 of this pocket guide.


- This is a summary of the AAN guideline on utility of surgical decompression for treating diabetic neuropathy. Surgical decompression of multiple peripheral nerves is being utilized as an alternative approach to treatment of symptomatic diabetic neuropathy (Dellon, 1992; Wieman & Patel, 1995; Aszmann et al., 2000; Tambwekar, 2001; Wood & Wood, 2003; Biddinger & Amend, 2004; Aszmann et al., 2004; Caffee, 2000). This is based on the hypothesis that diabetic nerves are more vulnerable to compressive injury at potential sites for entrapment (Lee & Dellon, 2003; Upton & McComas, 1973; Dellon & MacKinnon, 1991).

- More than 240 surgeons in 41 states in the United States and in 15 other countries have been trained to perform the decompressive surgery (Dellon, 2005). The controversial nature of this treatment, the large number of patients with diabetes mellitus (estimated 18.2 million in the United States), and the typically progressive and irreversible nature of diabetic neuropathy motivated the development of this guideline.

Recommendations

- Given current knowledge, this treatment is unproven (U*).

* Evidence rating key can be found on page 5 of this pocket guide.

Treatment of Postherpetic Neuralgia (2004; reaffirmed 2008)

This is a summary of the AAN guideline on treatment of postherpetic neuralgia (PHN). The guideline was developed to answer the following clinical question: In patients with PHN, which treatments provide benefit in terms of decreased pain and improved quality of life? PHN, persistence of the pain of herpes zoster more than 3 months after resolution of the rash, is relatively common, affecting 10% to 15% of those with herpes zoster. Zoster-associated pain is used to
describe the continuum of pain from acute herpes zoster to the development of PHN. The time interval used in the clinical case definition of PHN varies in the literature from 1 to 6 months after resolution of the rash. The incidence of PHN increases with age. The duration of PHN is highly variable. The natural history of resolution of PHN over time is a confounder in the evaluation of treatment efficacy and may limit the ability to generalize the results of controlled clinical trials in this population.

**Recommendations**

- Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of PHN (**A**

- In countries where preservative-free intrathecal methylprednisolone is available, it may be considered in the treatment of PHN (**A**).

- There is limited evidence to support nortriptyline over amitriptyline because of fewer side effects (**B**), and the data are insufficient to recommend one opioid over another. Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine.

- Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit (**B**).

- Aspirin in cream is possibly effective in the relief of pain in patients with PHN (**C**). The magnitude of benefit of aspirin in cream is low, as is seen with capsaicin (**A**).

- The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryoautery, topical piroxicam, extract of Ganoderma lucidum, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of PHN (**U**).

- There is insufficient evidence at this time to make any recommendations on the long-term effects of these treatments.

- Figure 16 presents treatment categories for PHN.
### Figure 16. Treatment categories for postherpetic neuralgia

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium to high efficacy, good strength of evidence, and low level of side effects</td>
<td>Lower efficacy than those listed in Group 1, or limited strength of evidence, or side effect concerns</td>
<td>Evidence indicating no efficacy compared to placebo</td>
<td>Reports of benefit limited to Class IV studies</td>
</tr>
</tbody>
</table>

- Gabapentin
- Lidocaine patch
- Oxycodone or morphine sulfate, controlled release
- Pregabalin
- Tricyclic antidepressants

- Aspirin in cream or ointment
- Capsaicin, topical
- Methylprednisolone, intrathecal†

- Acupuncture
- Benzydamine cream
- Dextromethorphan
- Indomethacin
- Lorazepam
- Methylprednisolone, epidural
- Vincristine iontophoresis
- Vitamin E
- Zimelidine

- Biperidin
- Carbamazepine
- Chlorprothixene
- Cryocaunetry
- Dorsal root entry zone lesion
- Extract of Ganoderma lucidum
- He:Ne laser irradiation
- Ketamine
- Methylprednisolone iontophoresis
- Morphine sulfate, epidural
- Nicardepine
- Piroxicam, topical
- Stellate ganglion block
- Triamcinolone, intralesional

†While there were no severe adverse effects in the reviewed studies, there is potential for chemical meningitis and arachnoiditis with the use of intrathecal methylprednisolone. Methylprednisolone is not approved by the US Food and Drug Administration for intrathecal use in this indication. The concurrent use of intrathecal lidocaine carries the risk of hypotension and respiratory depression. Therefore, these injections are best given by experienced medical personnel in a hospital setting.

* Evidence rating key can be found on page 5 of this pocket guide.

Neuropathy and Pain
Guidelines

The following pages summarize five AAN guidelines on Parkinson disease (PD) and/or other movement disorders:

Treatment of Nonmotor Symptoms of Parkinson Disease (Neurology 2010;74:924–931)

Botulinum Neurotoxin for the Treatment of Movement Disorders (Neurology 2008;70:1699–1706)

Treatment of Parkinson Disease with Motor Fluctuations and Dyskinesia (Neurology 2006;66:983–995)


Diagnosis and Prognosis of New Onset Parkinson Disease (Neurology 2006;66:968–975; reaffirmed October 2009)

Tools & Resources

For more information, please refer to www.aan.com to access the full guidelines and the following companion tools:

- Clinician Summaries
- Patient/Caregiver Summaries
- Slide Presentations
- Clinical Examples
- Posters
- Podcasts

Treatment of Nonmotor Symptoms of Parkinson Disease (2010)

Endorsed by the American Academy of Sleep Medicine.

This is a summary of the AAN guideline on treatment of nonmotor symptoms of Parkinson disease (PD). Nonmotor symptoms (sleep dysfunction, sensory symptoms, autonomic dysfunction, mood disorders, and cognitive abnormalities) in PD are a major cause of morbidity, yet are often underrecognized. This guideline evaluates treatment options for the nonmotor symptoms of PD. Articles pertaining to cognitive and mood dysfunction in PD, as well as treatment of sialorrhea with botulinum toxin, were previously reviewed as part of AAN guidelines and were not included here.

Recommendations

Autonomic Symptoms

- Sildenafil citrate may be considered in patients with PD with erectile dysfunction (ED) (C*).
• Clinical Context: A complete medical evaluation should determine whether other treatable causes of ED may be present, including other medical conditions or side effects of medications. The US Food and Drug Administration (FDA) has approved sildenafil citrate as a medication to treat impotence.

• There is insufficient evidence to support or refute treatments of orthostatic hypotension (OH) in PD (U).

• Clinical Context: Randomized controlled trials (RCTs) of mineralocorticoids, alpha-sympathomimetics, and pyridostigmine in patients with PD are lacking. However, their pharmacologic action is consistent with improvement in OH. The only medications that are currently FDA-approved to treat OH are midodrine and L-threo-dihydroxyphenylserine (L-threo-DOPS; Droxidopa), an orally active synthetic precursor of norepinephrine.

• There is insufficient evidence to support or refute treatments of urinary incontinence in PD (U).

• Clinical Context: Although RCTs of anticholinergics in patients with PD are lacking, their pharmacologic action and widespread clinical use are consistent with benefit in urinary incontinence. Anticholinergics have been shown to cause confusion in patients with PD.

• Isosmotic macrogol (polyethylene glycol) may be considered to treat constipation in PD (C).

• There is insufficient evidence to support or refute the use of botulinum toxin to treat constipation in PD (U).

• Clinical Context: Although RCTs of treatments for constipation in patients with PD are lacking, their pharmacologic action and widespread clinical use are consistent with benefit in constipation. Additionally, nonpharmacologic treatments such as increased water and dietary fiber intake have shown clinical benefit in relieving constipation. Drugs used to treat many conditions, including PD, can cause constipation.

• The use of botulinum toxin as a treatment for sialorrhea was reviewed as part of a previous AAN guideline, which concluded that botulinum toxin should be considered for drooling (B).

• Controlled trials evaluating treatment for other autonomic symptoms, including heat intolerance, urinary frequency, urinary urgency, nocturia, sweating, hypersalivation, drooling, seborrhea, hypersexuality, and leg edema, are lacking.

Sleep Dysfunction

• Modafinil should be considered for patients to improve their subjective perception of excessive daytime somnolence (EDS) (A).

• There is insufficient evidence to support or refute a safety benefit in patients with PD with EDS who engage in activities where sleepiness poses a potential danger (e.g., driving) (U). It should be noted that patients who are treated with modafinil may experience an improvement in sleep perception.
without an actual improvement in objective sleep measurements.

• There is insufficient evidence to support or refute the benefit of levodopa on objective sleep parameters that are not affected by motor status (U).

• There is insufficient evidence to support or refute the treatment of poor sleep quality with melatonin (U).

• Clinical Context: Deep brain stimulation (DBS) of the subthalamus (STN) is not currently used to treat sleep disorders.

• Levodopa/carbidopa should be considered to treat periodic limb movements of sleep (PLMS) (B).

• There is insufficient evidence to support or refute the treatment of restless legs syndrome (RLS) and PLMS with nonergot dopamine agonists (U).

• Clinical Context: Data on the use of dopamine agonists to treat RLS and PLMS specifically in patients with PD are lacking. The dopamine agonists ropinirole and pramipexole are the only FDA-approved agents for the treatment of moderate to severe primary RLS.

• There is insufficient evidence to support or refute the treatment of REM sleep behavior disorder (RBD) (U).

• Clinical Context: The antiepileptic drug clonazepam is often used to treat RBD in the general population.

Fatigue

• Methylphenidate may be considered in patients with fatigue (C).

• Clinical Context: Methylphenidate has the potential for abuse. Although there is no current evidence to suggest such a risk in PD, patients with PD do have a risk for dopamine dysregulation syndrome and impulse control disorders that share many clinical and functional imaging features with addiction. Regarding sleep disorders, there are currently no controlled studies on treatment for sleep apnea, sleep-disordered breathing, parasomnia, and sleepwalking.

Psychological Symptoms

• There is insufficient evidence to support or refute the treatment of anxiety in PD with levodopa (U).

• Clinical Context: Although RCTs of antianxiety agents in patients with PD are lacking, their pharmacologic action and widespread clinical use are consistent with benefit in anxiety. Antianxiety medications have been associated with ataxia, falls, and cognitive dysfunction. Controlled studies of treatment for other psychological symptoms, including obsessive behaviors, gambling, delusions, decreased motivation, apathy, and concentration difficulties, are lacking.

* Evidence rating key can be found on page 5 of this pocket guide.
Botulinum Neurotoxin for the Treatment of Movement Disorders (2008)

Endorsed by the American Academy of Physical Medicine and Rehabilitation and the American Association of Neuromuscular and Electrodiagnostic Medicine.

This is a summary of the AAN guideline on use of botulinum neurotoxin (BoNT) for treating movement disorders. BoNT has emerged as an effective treatment for numerous movement disorders associated with muscle overactivity. This guideline evaluates the current knowledge and evidence of BoNT in selected movement disorders.

**Recommendations**

**Blepharospasm**
- BoNT injection should be considered as a treatment option (B*).

**Hemifacial Spasm**
- BoNT injection may be considered as a treatment option (C).
- **Clinical Context:** The large magnitude of effects in the initial open-label studies likely has discouraged efforts to study BoNT in properly controlled clinical trials. Therefore, the evidence supporting BoNT use in blepharospasm and hemifacial spasm is suboptimal. No studies have compared BoNT with other major treatment alternatives, including oral pharmacologic and surgical therapies.

**Cervical Dystonia**
- BoNT injection should be offered as a treatment option (A).
- BoNT is probably more efficacious and better tolerated in CD patients than treatment with trihexyphenidyl (B).
- **Clinical Context:** Though commonly used for BoNT injection in CD, EMG localization technique is not established.

**Focal Limb Dystonia**
- BoNT injection should be considered as a treatment option (B).
- **Clinical Context:** Treatment of focal limb dystonia with BoNT presents challenges, particularly in achieving sufficient neuromuscular blockade to alleviate dystonic movements without causing excessive muscle weakness. While many clinicians advocate EMG or nerve stimulation guidance to optimize needle location for injection, further data are needed to establish a recommendation.

**Laryngeal Dystonia**
- BoNT injection should be considered as a treatment option for adductor spasmodic dysphonia (B).
- There is insufficient evidence to support or refute the use of BoNT in abductor spasmodic dysphonia (U).
• **Clinical Context:** The evidence supporting BoNT use in laryngeal disorders is suboptimal. While most clinicians utilize EMG targeting for laryngeal injections, the utility of this technique is not established in comparative trials. Dramatic results in the initial open-label studies and the lack of other effective therapy likely have discouraged efforts to study BoNT in larger and more properly controlled clinical trials.

**Motor Tics**

• BoNT injection may be considered as a treatment option (C).

• **Clinical Context:** There are no data to compare the efficacy of BoNT and neuroleptics in the treatment of tic disorders.

**Tremor**

• BoNT injection should be considered as a treatment option in patients with essential hand tremor who fail treatment with oral agents (B).

• **Clinical Context:** Oral agents and deep brain stimulation are alternative treatments for essential tremor. There are presently no data comparing the efficacy of BoNT to these treatment modalities. By reducing or eliminating BoNT injection into wrist extensors, the complications of finger and hand weakness may be reduced. There are no controlled data employing the new methodology.

* Evidence rating key can be found on page 5 of this pocket guide.

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**Neuroprotective Strategies and Alternative Therapies for Parkinson Disease** (2006; reaffirmed 2009)

This is a summary of the AAN guideline on neuroprotective strategies and alternative therapies for Parkinson disease (PD). Many nonstandard pharmacologic and nonpharmacologic therapies are currently employed by patients and caregivers. One study found that 63% of patients with PD use nutritional supplements, but fewer than 50% of patients reported this use to their physicians; only 4% were aware of possible drug supplement interactions. Additional nonpharmacologic therapies such as acupuncture, food supplements, naturopathic, nutraceuticals, and physical, occupational, and speech therapies are also in common use.

**Recommendations**

**Neuroprotective Strategies**

• For patients with PD, treatment with 2,000 units of vitamin E should not be considered for neuroprotection (B*).

• There is insufficient evidence to support or refute the long-term use of riluzole, coenzyme Q10, pramipexole, ropinirole, rasagiline, amantadine, or thalamotomy for neuroprotection (U).
Levodopa may be considered for initial treatment of PD (9 months), as it does not accelerate disease progression and is safe (B). There is no long-term evidence to recommend levodopa for neuroprotection (U).

As reviewed in a previous guideline, there is insufficient evidence to recommend the use of selegiline for neuroprotection (U).

**Alternative Therapies**

- There is insufficient evidence to support or refute the use of M pruriens (also known as cowhage or velvet bean) or fava beans for the treatment of motor symptoms of PD (U).
- For patients with PD, vitamin E (2,000 units) should not be considered for symptomatic treatment (B).
- There is insufficient evidence to support or refute the use of acupuncture in PD (U).
- There is insufficient evidence to support or refute manual therapy, biofeedback, or Alexander technique in the treatment of PD (U). The Alexander technique requires developing an awareness of posture in order to improve it.
- For patients with PD, exercise therapy may be considered to improve function (C).
- For patients with PD complicated by dysarthria, speech therapy may be considered to improve speech volume (C).

* Evidence rating key can be found on page 5 of this pocket guide.

**Treatment of Parkinson Disease with Motor Fluctuations and Dyskinesia** (2006; reaffirmed 2009)

This is a summary of the AAN guideline on treatment of Parkinson disease (PD) with motor fluctuations and dyskinesia. Motor fluctuations and dyskinesia can be resistant to medical therapy. This, along with advances in the understanding of basal ganglia circuitry, surgical techniques, neuroimaging, and intraoperative microelectrode recording, has led to a resurgence in surgical approaches for medically refractory disabilities. Initially, ablative procedures like thalamotomy and pallidotomy were used to treat PD symptoms. However, due to concerns about morbidity, especially with bilateral procedures, deep brain stimulation (DBS) has become the most commonly performed surgery for PD in North America.

**Medical Treatment**

- Although initially effective, dopaminergic therapies are eventually complicated by motor fluctuations, including off time (periods of return of PD symptoms when medication effect wears off) and dyskinesia (drug-induced involuntary movements) in most patients.
Risk Factors for Motor Complications

- Younger age at onset of PD
- Disease severity
- Higher levodopa dosage
- Longer disease duration

Surgical Treatment

Motor fluctuations and dyskinesia can be resistant to medical therapy. This, along with advances in the understanding of basal ganglia circuitry, surgical techniques, neuroimaging, and intraoperative microelectrode recording, has led to the resurgence of surgical approaches for medically refractory disabilities.

Deep Brain Stimulation

DBS is a stereotactic surgical procedure that uses an implanted electrode connected to an implantable pulse generator (IPG) that delivers electrical current to a targeted nucleus in the brain. The following are recommendations for DBS and factors that predict improvement after this procedure.

Recommendations

Medical Treatment

For patients with PD with motor fluctuations, the available evidence suggests:

- Entacapone and rasagiline should be offered to reduce off time (A*).
- Pergolide, pramipexole, ropinirole, and tolcapone should be considered to reduce off time (B). Tolcapone (hepatotoxicity) and pergolide (valvular fibrosis) should be used with caution and require monitoring.
- Apomorphine (injected subcutaneously), cabergoline, and selegiline may be considered to reduce off time (C).
- Sustained-release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (C).
- Ropinirole may be chosen over bromocriptine for reducing off time (C). Otherwise, there is insufficient evidence to recommend one agent over another (U).
- Amantadine may be considered for patients with PD with motor fluctuations in reducing dyskinesia (C).
- There is insufficient evidence to support or refute the efficacy of clozapine in reducing dyskinesia (U). Clozapine’s potential toxicity including agranulocytosis, seizures, myocarditis and orthostatic hypotension with or without syncope, and required white blood cell count monitoring must be considered.

Deep Brain Stimulation

- DBS of the subthalamic nucleus (STN) may be considered as a treatment option in PD patients to improve motor function and to reduce motor
fluctuations, dyskinesia, and medication usage (C). Patients need to be counseled regarding the risks and benefits of this procedure.

- There is insufficient evidence to make any recommendations about the effectiveness of DBS of the globus pallidus interna (GPI) or ventral intermediate (VIM) nucleus of the thalamus in reducing motor complications or medication usage, or in improving motor function in PD patients (U).
- Preoperative response to levodopa should be considered as a factor predictive of outcome after DBS of the STN (B).
- Age and duration of PD may be considered as factors predictive of outcome after DBS of the STN. Younger patients with shorter disease durations may possibly have improvement greater than that of older patients with longer disease durations (C).
- There is insufficient evidence to make any recommendations about factors predictive of improvement after DBS of the GPI or of VIM nucleus of the thalamus in PD patients (U).

Note: Strength indicates level of supporting evidence, not a hierarchy of efficacy.

* Evidence rating key can be found on page 5 of this pocket guide.

Diagnosis and Prognosis of New Onset Parkinson Disease (2006; reaffirmed 2009)

This is a summary of the AAN guideline on diagnosis and prognosis of new onset Parkinson disease (PD). Knowledge of the features that predict the rate of PD progression would empower clinicians to better counsel patients regarding prognosis and life expectancy. Improvement in diagnostic accuracy and the ability to predict the rate of progression would also impact on the ability to assess neuroprotective therapies that may delay the progression of the disease.

Recommendations

**Diagnosis**

Determining the presence of the following clinical features in early stages of disease should be considered to distinguish other parkinsonian syndromes from PD (B*). The following probably are useful in distinguishing other parkinsonian syndromes from PD:

- Falls at presentation and early in the disease course
- Poor response to levodopa
- Symmetry at onset
- Rapid progression (to Hoehn and Yahr stage 3 in 3 years)
- Lack of tremor
- Dysautonomia (urinary urgency/incontinence and fecal incontinence, urinary retention requiring catheterization, persistent erectile failure or symptomatic orthostatic hypotension)
• Levodopa and apomorphine challenge should be considered for confirmation when the diagnosis of PD is in doubt (B).

• Because olfaction is frequently impaired in PD, olfaction testing should be considered to differentiate PD from progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), but not PD from multiple system atrophy (MSA) (B).

• There is insufficient evidence to determine whether levodopa and apomorphine challenge or olfaction testing have any advantage over the clinical diagnostic criteria of PD (U). Additionally, there is insufficient evidence to determine the optimal combination or sequence of these tests (U).

The following may not be useful in differentiating PD from other parkinsonian syndromes (C):

• Growth hormone (GH) stimulation with clonidine
• Electrooculography
• Single photon emission computed tomography (SPECT) scanning

There is insufficient evidence to support or refute the following as a means of distinguishing PD from other parkinsonian syndromes (U):

• Urodynamics
• Autonomic testing
• Urethral or anal EMG
• MRI
• Brain parenchyma sonography
• 18F Fluorodeoxyglucose (FDG) PET

**Prognosis**

• In patients with newly diagnosed PD, older age at onset and rigidity/hypokinesia as an initial symptom should be used to predict more rapid rate of motor progression (B).

• The presence of associated comorbidities (stroke, auditory deficits, and visual impairments), postural instability/gait difficulty (PIGD), and male gender may be used to predict faster rate of motor progression (C).

• Tremor as a presenting symptom may be used to predict a more benign course and longer therapeutic benefit to levodopa (C).

• Older age at onset and initial hypokinesia/rigidity should be used to predict earlier development of cognitive decline and dementia (B).

• Older age of onset, dementia, and decreased dopamine responsiveness may be used to predict earlier nursing home placement as well as decreased survival (C).

*Evidence rating key can be found on page 5 of this pocket guide.*
Guidelines

The following pages summarize five AAN guidelines on stroke and/or vascular neurology:

Diffusion and Perfusion MRI for the Diagnosis of Acute Ischemic Stroke (*Neurology* 2010;75:177–185)


Assessment of Transcranial Doppler Ultrasonography (*Neurology* 2004;62;1468–1481; reaffirmed November 2007)


Tools & Resources

Please refer to www.aan.com to access the full guidelines and the following companion tools:

- Clinician Summaries
- Patient/Caregiver Summaries
- Slide Presentations
- Background/Data

Diffusion and Perfusion MRI for the Diagnosis of Acute Ischemic Stroke (2010)

This is a summary of the AAN guideline on two types of MRI for the diagnosis of acute ischemic stroke. Noncontrast CT is the current diagnostic standard for acute stroke due to its wide availability and presumed near-perfect sensitivity for acute intracerebral hemorrhage (ICH), the most important differential diagnosis to ischemic stroke. The sensitivity of CT in acute ischemic stroke varies. As noncontrast CT has limited sensitivity for the diagnosis of ischemic stroke in the initial hours, improved accuracy of stroke diagnosis is necessary for the development and application of optimal thrombolytic and other stroke therapy.

Recommendations

- Diffusion-weighted imaging (DWI) should be considered superior to noncontrast CT scan for the diagnosis of acute ischemic stroke in patients presenting within 12 hours of symptom onset (A*).
- There is insufficient evidence to support or refute the value of perfusion-weighted imaging (PWI) in diagnosing acute ischemic stroke (U).
• Baseline DWI volume should be considered useful in predicting baseline clinical stroke severity and final lesion volume in anterior-circulation stroke syndromes (B).

• Baseline DWI volume may be considered not useful in predicting baseline National Institutes of Health Stroke Scale (NIHSS) score in posterior-circulation stroke syndromes (C).

• Baseline DWI volume may be considered useful in predicting clinical outcome as measured by the NIHSS and Barthel Index (C).

• Baseline PWI volume may be considered useful in predicting baseline clinical stroke severity (C).

Clinical Context

• In patients presenting with acute neurologic impairment, noncontrast CT imaging is used to evaluate for infarct and to exclude hemorrhage and other structural lesions that may mimic stroke. The evidence demonstrates that DWI is accurate and superior to CT for the diagnosis of acute ischemic stroke relative to clinical and imaging outcomes. However, in clinical practice, the availability and cost of imaging modalities and the requirements of medical management enter into the decision about which test to perform in the acute period.

• The true sensitivity of DWI for the diagnosis of ischemic stroke is not 100% and is probably closer to 80%–90% in a general sample of patients presenting for emergency evaluation of possible stroke. Many of the initial case series and small CT comparative studies reported a near-100% sensitivity for DWI in the hyperacute stage of stroke in highly selected subsets of patients. Increasingly, however, cases of DWI-negative stroke were reported. False-negative DWI in ischemic stroke may be attributable to mild (small) strokes, brainstem location, and the earliest times from onset, and may become less frequent as imaging technology continues to improve.

• DWI-positive scans in TIA are common. According to the literature, acute ischemic DWI lesions are present in 40.1% of patients with the clinical diagnosis of a TIA, a finding that correlates with symptom duration. Only one of the studies involved DWI performed within 24 hours of symptom onset. A recent study estimated the epidemiologic impact of DWI-based diagnosis would result in reduced annual TIA incidence (33%) and increased stroke incidence (7%) in the United States.

* Evidence rating key can be found on page 5 of this pocket guide.

Carotid Endarterectomy (2005; reaffirmed 2008)

• This is a summary of the AAN guideline on carotid endarterectomy (CE). CE reduces the stroke risk compared to medical therapy alone for patients with 70% to 99% symptomatic stenosis (16% absolute risk reduction at 5 years). There is a smaller benefit for patients with 50% to 69% symptomatic stenosis (absolute risk reduction 4.6% at 5 years). There is a small benefit for asymptomatic patients with 60% to 99% stenosis if the perioperative
complication rate is low. Aspirin in a dose of 81 to 325 mg per day is preferred vs higher doses (650 to 1,300 mg per day) in patients undergoing endarterectomy.

**Recommendations**

- CE is generally beneficial for recently symptomatic (within previous 6 months) patients with 70% to 99% internal carotid artery (ICA) angiographic stenosis (A*). CE should not be considered for symptomatic patients with less than 50% stenosis (A). CE may be considered for patients with 50% to 69% symptomatic stenosis (B), but the clinician should consider additional clinical and angiographic variables (C). It is recommended that the patient have at least a 5-year life expectancy and that the perioperative stroke/death rate should be <6% for symptomatic patients (A). Medical management is preferred to CE for symptomatic patients with <50% stenosis (A).

- It is reasonable to consider CE for patients between the ages of 40 and 75 years and with asymptomatic stenosis of 60% to 99% if the patient has an expected 5-year life expectancy and if the surgical stroke or death frequency can be reliably documented to be <3% (A). The 5-year life expectancy is important since perioperative strokes pose an up-front risk to the patient and the benefit from CE emerges only after a number of years.

- No recommendation can be provided regarding the value of emergent CE in patients with a progressing neurologic deficit (U).

- Clinicians should consider patient variables in CE decision making. Women with 50% to 69% symptomatic stenosis did not show clear benefit in previous trials. In addition, patients with hemispheric TIA/stroke had greater benefit from CE than patients with retinal ischemic events (C). Clinicians should also consider several radiologic factors in decision making about CE. For example, contralateral occlusion erases the small benefit of CE in asymptomatic patients (C), whereas in symptomatic patients, it is associated with increased operative risk but persistent benefit (C). CE for patients with angiographic near-occlusion in symptomatic patients is associated with a trend toward benefit at 2 years but not associated with a clear long-term benefit (C). Patients operated on within 2 weeks of their last TIA or mild stroke derive greater benefit from CE (C).

- Symptomatic and asymptomatic patients undergoing CE should be given aspirin (81 or 325 mg/day) prior to surgery and for at least 3 months following surgery to reduce the combined endpoint of stroke, myocardial infarction, and death (A). Although data are not available, it is recommended that aspirin (81 or 325 mg/day) be continued indefinitely, provided that contraindications are absent. Aspirin at 650 or 1,300 mg/day is less effective in the perioperative period. The data are insufficient to recommend the use of other antiplatelet agents in the perioperative setting.

- At this time the available data are insufficient to declare either CE before or simultaneous with coronary artery bypass graft (CABG) as superior in
patients with concomitant carotid and coronary artery occlusive disease (U).

- For patients with severe stenosis and a recent TIA or nondisabling stroke, CE should be performed without delay, preferably within 2 weeks of the patient’s last symptomatic event (C). There is insufficient evidence to support or refute the performance of CE within 4 to 6 weeks of a recent moderate to severe stroke (U).

* Evidence rating key can be found on page 5 of this pocket guide.

**Assessment of Transcranial Doppler Ultrasonography** (2004; reaffirmed 2007)

This is a summary of the AAN guideline that assesses transcranial Doppler (TCD) ultrasonography. TCD can be performed at the bedside and repeated as needed or applied for continuous monitoring; it is frequently less expensive than other techniques; and contrast agents are not used. A chief limitation is it can demonstrate cerebral blood flow velocities only in certain segments of large intracranial vessels (arterial disease commonly occurs at these locations). The reference standard vs TCD must be appropriate to the clinical setting. Table 3 presents data on the clinical utility of TCD.

**Table 3. Clinical Utility of TCD**

<table>
<thead>
<tr>
<th>TCD is able to provide information, and clinical utility is established.</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell disease</td>
<td>Screening of children aged 2–16 years with sickle cell disease for assessing stroke risk (A*), although the optimal frequency of testing is unknown (U).</td>
<td>86</td>
</tr>
<tr>
<td>Angiographic vasospasm</td>
<td>Detection and monitoring of angiographic vasospasm after spontaneous subarachnoid hemorrhage (A). More data are needed to show if its use affects clinical outcomes (U).</td>
<td></td>
</tr>
<tr>
<td>Intracranial ICA</td>
<td>25–30</td>
<td>83–91</td>
</tr>
<tr>
<td>MCA</td>
<td>39–94</td>
<td>70–100</td>
</tr>
<tr>
<td>ACA</td>
<td>13–71</td>
<td>65–100</td>
</tr>
<tr>
<td>VA</td>
<td>44–100</td>
<td>82–88</td>
</tr>
<tr>
<td>BA</td>
<td>77–100</td>
<td>42–79</td>
</tr>
<tr>
<td>PCA</td>
<td>48–60</td>
<td>78–87</td>
</tr>
</tbody>
</table>

ICA = internal carotid artery; MCA = middle cerebral artery; ACA = anterior cerebral artery; VA = vertebral artery; BA = basilar artery; PCA = posterior cerebral artery.
TCD is able to provide information, but clinical utility compared to other diagnostic tools remains to be determined.

<table>
<thead>
<tr>
<th>Intracranial steno-occlusive disease</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCD is probably useful (B*) for the evaluation of occlusive lesions of intracranial arteries in the basal cisterns (especially the ICA siphon and MCA). The relative value of TCD compared with MR angiography or CT angiography remains to be determined (U). Data are insufficient to recommend replacement of conventional angiography with TCD (U).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>70–90</td>
<td>90–95</td>
</tr>
<tr>
<td>Posterior circulation occlusion</td>
<td>50–80</td>
<td>80–96</td>
</tr>
<tr>
<td>MCA occlusion</td>
<td>85–95</td>
<td>90–98</td>
</tr>
<tr>
<td>ICA, VA, BA occlusion</td>
<td>55–81</td>
<td>96</td>
</tr>
<tr>
<td>Cerebral circulatory arrest (adjunctive test in the determination of brain death)</td>
<td>If needed, TCD can be used as a confirmatory test, in support of a clinical diagnosis of brain death (A).</td>
<td>91–100</td>
</tr>
</tbody>
</table>
TCD is able to provide information, but clinical utility remains to be determined.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral thrombolysis</td>
<td>TCD is probably useful for monitoring thrombolysis of acute MCA occlusions (B). More data are needed to assess the frequency of monitoring for clot dissolution and enhanced recanalization and to influence therapy (U).</td>
<td></td>
</tr>
<tr>
<td>Complete occlusion</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Partial occlusion</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>Recanalization</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>Cerebral microembolism detection</td>
<td>TCD monitoring is probably useful for the detection of cerebral microembolic signals in a variety of cardiovascular/cerebrovascular disorders/procedures (B). Data do not support the use of this TCD technique for diagnosis or monitoring response to antithrombotic therapy in ischemic cerebrovascular disease (U).</td>
<td></td>
</tr>
<tr>
<td>Carotid endarterectomy (CEA)</td>
<td>TCD monitoring is probably useful to detect hemodynamic and embolic events that may result in perioperative stroke during and after CEA in settings where monitoring is felt to be necessary (B).</td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass graft (CABG) surgery</td>
<td>TCD monitoring is probably useful (B) during CABG for detection of cerebral microemboli. TCD is possibly useful to document changes in flow velocities and CO₂ reactivity during CABG surgery (C). Data are insufficient regarding the clinical impact of this information (U).</td>
<td></td>
</tr>
<tr>
<td>Vasomotor reactivity testing</td>
<td>TCD is probably useful (B) for the detection of impaired cerebral hemodynamics in patients with severe (&gt;70%) asymptomatic extracranial ICA stenosis, symptomatic or asymptomatic extracranial ICA occlusion, and cerebral small-artery disease. Whether these techniques should be used to influence therapy and improve patient outcomes remains to be determined (U).</td>
<td></td>
</tr>
<tr>
<td>Vasospasm (VSP) after traumatic subarachnoid hemorrhage (SAH)</td>
<td>TCD is probably useful for the detection of VSP following traumatic SAH (B), but data are needed to show its accuracy and clinical impact in this setting (U).</td>
<td></td>
</tr>
<tr>
<td>TCCS</td>
<td>TCCS is possibly useful (C) for the evaluation and monitoring of space-occupying ischemic MCA infarctions. More data are needed to show if it has value vs. CT and MRI scanning and if its use affects clinical outcomes (U).</td>
<td></td>
</tr>
</tbody>
</table>

104 Stroke and Vascular Neurology
TCD is able to provide information, but other diagnostic tests are typically preferable.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right-to-left cardiac shunts</td>
<td>70–100</td>
<td>&gt;95</td>
</tr>
<tr>
<td>Extracranial ICA stenosis</td>
<td>3–95</td>
<td>60–100</td>
</tr>
<tr>
<td>TCD battery</td>
<td>49–78</td>
<td>42–100</td>
</tr>
<tr>
<td>TCD battery and carotid duplex</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>Contrast-enhanced TCCS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TEE = transesophageal echocardiography

* Evidence rating key can be found on page 5 of this pocket guide.


This is a summary of the AAN guideline on the risk of subsequent stroke or death in patients with a cryptogenic stroke and a patent foramen ovale (PFO) or an atrial septal aneurysm (ASA).

**Recommendations**

**Prognosis**

- For patients who have had a cryptogenic stroke and have a PFO, the evidence indicates that the risk of subsequent stroke or death is no different from other cryptogenic stroke patients without PFO when treated medically with antiplatelet agents or anticoagulants. Therefore, in persons with a cryptogenic stroke receiving such therapy, neurologists should communicate to patients and their families that presence of PFO does not confer an increased risk for subsequent stroke compared to other cryptogenic stroke patients without atrial abnormalities (A*).

- However, it is possible that the combination of PFO and atrial septal aneurysm confers an increased risk of subsequent stroke in medically treated patients who are less than 55 years of age. Therefore, in younger
stroke patients, studies that can identify PFO or atrial septal aneurysm may be considered for prognostic purposes (C).

**Therapy**

- Among patients with a cryptogenic stroke and atrial septal abnormalities, there is insufficient evidence to determine the superiority of aspirin or warfarin for prevention of recurrent stroke or death (U).
- There is insufficient evidence regarding the effectiveness of either surgical or percutaneous closure of PFO (U).
- Among patients with a cryptogenic stroke and atrial septal abnormalities, the risks of minor bleeding are possibly greater with warfarin (C).

*Evidence rating key can be found on page 5 of this pocket guide.*


This is a summary of a guideline that was developed as an educational service of the AAN and the American Stroke Association of the American Heart Association.

**Recommendations**

- Patients with acute ischemic stroke presenting within 48 hours of symptom onset should be given aspirin (160 to 325 mg/day) to reduce stroke mortality and decrease morbidity, provided contraindications such as allergy and gastrointestinal bleeding are absent, and the patient has not or will not be treated with recombinant tissue-type plasminogen activator (A*). The data are insufficient at this time to recommend the use of any other platelet antiaggregant in the setting of acute ischemic stroke.

- Subcutaneous unfractionated heparin, low molecular weight (LMW) heparins, and heparinoids may be considered for deep vein thrombosis (DVT) prophylaxis in at-risk patients with acute ischemic stroke, recognizing that nonpharmacologic treatments for DVT prevention also exist (A). A benefit in reducing the incidence of pulmonary embolism (PE) has not been demonstrated. The relative benefits of these agents must be weighed against the risk of systemic and intracerebral hemorrhage.

- Although there is some evidence that fixed-dose, subcutaneous, unfractionated heparin reduces early recurrent ischemic stroke, this benefit is negated by a concomitant increase in the occurrence of hemorrhage. Therefore, use of subcutaneous unfractionated heparin is not recommended for decreasing the risk of death or stroke-related morbidity or for preventing early stroke recurrence (A).
• Dose-adjusted, unfractionated heparin is not recommended for reducing morbidity, mortality, or early recurrent stroke in patients with acute stroke (i.e., in the first 48 hours) because the evidence indicates it is not efficacious and may be associated with increased bleeding complications (B).

• High-dose LMW heparin/heparinoids have not been associated with either benefit or harm in reducing morbidity, mortality, or early recurrent stroke in patients with acute stroke and are, therefore, not recommended for these goals (A).

• IV, unfractionated heparin, or high-dose LMW heparin/heparinoids are not recommended for any specific subgroup of patients with acute ischemic stroke that is based on any presumed stroke mechanism or location (e.g., cardioembolic, large vessel atherosclerotic, vertebrobasilar, or progressing stroke) because data are insufficient (U). Although the LMW heparin, dalteparin, at high doses may be efficacious in patients with atrial fibrillation, it is not more efficacious than aspirin in this setting. Because aspirin is easier to administer, aspirin, rather than dalteparin, is recommended for the various stroke subgroups (A).

• Figure 17 summarizes the guideline research results.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Benefit data</th>
<th>Risk data</th>
<th>Compared with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>• Prevention of early recurrent ischemic stroke (CAST, IST)</td>
<td>• Small increase in intracerebral hemorrhage or hemorrhagic transformation (CAST, IST, MAST)</td>
<td>• Compared with placebo/no aspirin</td>
</tr>
<tr>
<td></td>
<td>• Small benefit in reducing death and dependence (CAST, IST, MAST)</td>
<td>• Small increase in transfused or fatal extracranial hemorrhage (IST, CAST)</td>
<td></td>
</tr>
<tr>
<td>IV unfractionated heparin</td>
<td>• Inadequate data</td>
<td>• Inadequate data</td>
<td></td>
</tr>
<tr>
<td>SQ unfractionated heparin</td>
<td>• Small benefit in reducing early recurrent stroke outweighed by small increase in CNS hemorrhage (IST)</td>
<td>• Increase in symptomatic CNS hemorrhage (8/1,000 treated, IST)</td>
<td>• Compared with no subcutaneous heparin (50% on ASA, 50% on no ASA; IST)</td>
</tr>
<tr>
<td></td>
<td>• No benefit in reducing morbidity, mortality (IST)</td>
<td>• Increase in fatal or transfused systemic hemorrhage (9/1,000 treated, IST)</td>
<td>• Compared to no subcutaneous heparin (McCarthy and Turner)</td>
</tr>
<tr>
<td></td>
<td>• Reduce PE and DVT (IST, McCarthy and Turner)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMW heparins/heparinoids</td>
<td>• Benefit in reducing 6-month morbidity (nadroparin, Kay et al.)</td>
<td>• Variable increase in systemic and CNS hemorrhage across studies (Kay et al., TOAST, Berge)</td>
<td>• Kay et al. and TOAST compared with placebo</td>
</tr>
<tr>
<td></td>
<td>• No benefit in reducing 3-month morbidity (TOAST)</td>
<td></td>
<td>• Berge compared with aspirin</td>
</tr>
<tr>
<td></td>
<td>• Reduces DVT (TOAST)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CAST = The Chinese Acute Stroke Trial; IST = The International Stroke Trial; MAST = The Multicentre Acute Stroke Trial–Italy; TOAST = Trial of the Heparinoid ORG 10172 in Acute Stroke

* Evidence rating key can be found on page 5 of this pocket guide.
All Current AAN Guidelines and Tools Available at www.aan.com

The guideline titles below are presented as they appear by topic area at www.aan.com. Some are cross-referenced in one or more topic areas.

**Brain Injury and Brain Death**
- Jun 2010  Update: Determining Brain Death in Adults
- Jul 2006  Prediction of Outcome in Comatose Survivors after Cardiopulmonary Resuscitation
- Jan 2003  Antiepileptic Drug Prophylaxis in Severe Traumatic Brain Injury

**Child Neurology**
- Jan 2010  Pharmacologic Treatment of Spasticity in Children and Adolescents with Cerebral Palsy
- Sep 2009  Evaluation of the Child with Microcephaly
- Nov 2006  Diagnostic Assessment of the Child with Status Epilepticus
- Jul 2006  Prediction of Outcome in Comatose Survivors after Cardiopulmonary Resuscitation
- Sep 2005  Use of Serum Prolactin in Diagnosing Epileptic Seizures
- Jan 2005  Corticosteroid Treatment of Duchenne Dystrophy
- Dec 2004  Pharmacological Treatment of Migraine Headache in Children and Adolescents
- Mar 2004  Diagnostic Assessment of the Child with Cerebral Palsy
- Sep 2003  Immunotherapy for Guillain-Barré Syndrome
- Mar 2003  Temporal Lobe and Localized Neocortical Resections for Epilepsy
- Jan 2003  Antiepileptic Drug Prophylaxis in Severe Traumatic Brain Injury
- Jan 2003  Treatment of the Child with a First Unprovoked Seizure
- Aug 2002  Evaluation of Children and Adolescents with Recurrent Headache
- Sep 2000  Evaluating the First Nonfebrile Seizure in Children
- Aug 2000  Screening and Diagnosis of Autism

**Dementia**
- Apr 2010  Update: Evaluation and Management of Driving Risk in Dementia

*Replaces Risk of Driving and Alzheimer’s Disease (2000).*
Apr 2006  Treatment of Parkinson Disease with Motor Fluctuations and Dyskinesias
Apr 2006  Diagnosis and Prognosis of New Onset Parkinson Disease

**Multiple Sclerosis**

May 2010  Efficacy and Safety of Mitoxantrone (Novantrone) in the Treatment of Multiple Sclerosis
Sep 2008  Use of Natalizumab (Tysabri) for the Treatment of Multiple Sclerosis
Mar 2007  Neutralizing Antibodies to Interferon-beta: Assessment of Their Clinical and Radiographic Impact
Nov 2003  The Use of Mitoxantrone (Novantrone) for the Treatment of Multiple Sclerosis
Sep 2003  Utility of MRI in Suspected MS
Feb 2002  Disease Modifying Therapies in Multiple Sclerosis
          *Replaces Practice Advisory on Selection of Patients with Multiple Sclerosis for Treatment with Betaseron.*
May 2000  Usefulness of Evoked Potentials in Identifying Clinically Silent Lesions in Patients with Suspected Multiple Sclerosis

**Neuromuscular**

Feb 2010  Symptomatic Treatment for Muscle Cramps
Oct 2009  Update: The Care of the Patient with Amyotrophic Lateral Sclerosis: Drug, Nutritional, and Respiratory Therapies
Oct 2009  Update: The Care of the Patient with Amyotrophic Lateral Sclerosis: Multidisciplinary Care, Symptom Management, and Cognitive/Behavioral Impairment
Jan 2009  Evaluation of Distal Symmetric Polyneuropathy: Role of Laboratory and Genetic Testing
Jan 2009  Evaluation of Distal Symmetric Polyneuropathy: Role of Autonomic Testing, Nerve Biopsy, and Skin Biopsy
Jun 2007  The Medical Treatment of Ocular Myasthenia
Jun 2006  Utility of Surgical Decompression for Treatment of Diabetic Neuropathy
Jan 2005  Distal Symmetric Polyneuropathy: A Definition for Clinical Research
Sep 2003  Immunotherapy for Guillain-Barré Syndrome
Mar 2003  Quantitative Sensory Testing
Jul 2000  Thymectomy for Autoimmune Myasthenia Gravis
Sep 1999  Electrodiagnostic Studies in Ulnar Neuropathy at the Elbow
Stroke and Vascular Neurology

Jul 2010  The Role of Diffusion and Perfusion MRI for the Diagnosis of Acute Ischemic Stroke

Sep 2005  Carotid Endarterectomy

May 2004  Transcranial Doppler Ultrasonography

Apr 2004  Recurrent Stroke in Patients with Patent Foramen Ovale and Atrial Septal Aneurysm

Jul 2002  Anticoagulants and Antiplatelet Agents in Acute Ischemic Stroke

Technology Assessments

Jan 2010  Efficacy of Transcutaneous Electric Nerve Stimulation in the Treatment of Pain in Neurologic Disorders

May 2008  Botulinum Neurotoxin for the Treatment of Movement Disorders

May 2008  Botulinum Neurotoxin for the Treatment of Spasticity

May 2008  Botulinum Neurotoxin in the Treatment of Autonomic Disorders and Pain

Sep 2005  Use of Serum Prolactin in Diagnosing Epileptic Seizures

Aug 2005  Addendum: Prevention of Post-Lumbar Puncture Headaches

Sep 2005  Carotid Endarterectomy

May 2004  Transcranial Doppler Ultrasonography

Oct 2000  Prevention of Post-Lumbar Puncture Headache

Aug 1998  Review of the Literature on Spinal Ultrasound for the Evaluation of Back Pain and Radicular Disorders

Jul 1997  Digital EEG, Quantitative EEG, and EEG Brain Mapping

Other

Oct 2008  The Diagnostic Evaluation and Treatment of Trigeminal Neuralgia

May 2008  Therapies for Benign Paroxysmal Positional Vertigo

Feb 2008  Assessing Patients in a Neurology Practice for Risk of Falls

Jul 2007  Treatment of Nervous System Lyme Disease

Mar 2007  Use of Epidural Steroid Injections to Treat Radicular Lumbosacral Pain

Aug 2005  Addendum: Prevention of Post-Lumbar Puncture Headaches
Jan 2005  Distal Symmetric Polyneuropathy: A Definition for Clinical Research
Sep 2004  Treatment of Postherpetic Neuralgia
Oct 2000  Prevention of Post-Lumbar Puncture Headache
Jul 2000  Thymectomy for Autoimmune Myasthenia Gravis
May 2000  Anticonvulsant Prophylaxis in Patients with Newly Diagnosed Brain Tumors
Jan 1998  Evaluation and Management of Intracranial Mass Lesions in AIDS
Jun 1997  Silicone Breast Implants and Neurologic Disorders
Mar 1996  Diagnosis of Patients with Nervous System Lyme Borreliosis (Lyme Disease)

All AAN Guidelines Being Updated
Apr 2006  Evaluation and Treatment of Depression, Psychosis, and Dementia in Parkinson Disease
Jun 2005  Therapies for Essential Tremor
May 2004  Medical Treatment of Infantile Spasms
Apr 2004  Efficacy and Tolerability of the New Antiepileptic Drugs I: Treatment of New Onset Epilepsy
Apr 2004  Efficacy and Tolerability of the New Antiepileptic Drugs II: Treatment of Refractory Epilepsy
Feb 2003  Evaluation of the Child with Global Developmental Delay
Sep 2002  Immunization and Multiple Sclerosis: A Summary of Published Evidence and Recommendations
Jun 2002  Neuroimaging of the Neonate
Jan 2002  Initiation of Treatment for Parkinson Disease
Replaces Initial Therapy of Parkinson Disease (Summary Statement) (1993).
May 2001  Detection of Dementia and Mild Cognitive Impairment
May 2001  Diagnosis of Dementia
May 2001  Management of Dementia
Apr 2001  Steroids, Acyclovir, and Surgery for Bell’s Palsy
Nov 2000  Vestibular Testing Techniques in Adults and Children
Sep 2000  Evidence-based Guidelines for Migraine Headache

Appendix 113
Sep 1999  Reassessment: Vagus Nerve Stimulation for Epilepsy
          Supplement to Assessment of Vagus Nerve Stimulation for Epilepsy (1997).
Jun 1999  The Relationship of MS to Physical Trauma and Psychological Stress
May 1999  Neurologic Risk of Immunization
Sep 1998  Stroke Prevention in Patients with Nonvalvular Atrial Fibrillation
Mar 1997  The Management of Concussion in Sports
Sep 1996  Thrombolytic Therapy for Acute Ischemic Stroke Practice Advisory
Sep 1996  Plasmapheresis
Mar 1996  Clinical Autonomic Testing
May 1995  Assessment and Management of Patients in the Persistent Vegetative State
Mar 1995  Determining Brain Death in Adults
Mar 1994  Melodic Intonation Therapy
Feb 1992  Techniques in the Diagnosis and Management of Sleep Disorders