Care of the Patient with Amyotrophic Lateral Sclerosis (ALS): Evidence-Based Guidelines for Your Practice

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Practice Parameter Update: The Care of the Patient with Amyotrophic Lateral Sclerosis (An Evidence-Based Review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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The American Academy of Neurology’s Guideline Development Process

A Brief Overview

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Practice Guidelines

Systematically and transparently developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.
AAN Guidelines are Evidence-Based

Consensus-based → Evidence-based
AAN Guidelines are Evidence-Based
Evidence-Based Process

1. Question
2. Evidence
3. Conclusion
4. Recommendation
For patients with ALS

Does riluzole vs. no riluzole

Prolong survival?
Evidence-Based Process

1. Question
2. Evidence
3. Conclusion
4. Recommendation
Finding All of the Evidence

A priori inclusion criteria

Search
Review abstracts
Review full text
Select articles
Finding ALS Evidence

- Databases: OVID, MEDLINE EMBASE, CINAHL
- Search terms:
  - ALS and its synonyms AND
  - Intervention term (e.g., riluzole)
- Inclusion criteria:
  - Relevant to the clinical questions
  - Limited to human subjects
- Exclusion criteria:
  - Articles related to postpolio conditions, cancer, or non-ALS disease
  - Articles not peer-reviewed
Rating the Evidence

Randomized Masked Trial  Single Case Report

Strong  Weak

Class I  Class II  Class III  Class IV
Classification of Evidence

For Therapeutic Questions

- Class I: A randomized, controlled clinical trial with near complete follow-up and masked outcome assessment.
- Class II: A flawed randomized controlled trial or matched cohort study with masked outcome assessment.
- Class III: A cohort study with independent outcome assessment.
- Class IV: Studies not meeting above criteria.
Evidence-Based Process

1. Question
2. Evidence
3. Conclusion
4. Recommendation
### Believe the Best Evidence

<table>
<thead>
<tr>
<th>Strength of Evidence</th>
<th>Wording of Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 + consistent Class I</td>
<td>“Established as”</td>
</tr>
<tr>
<td>2 + consistent Class II</td>
<td>“Probably”</td>
</tr>
<tr>
<td>2 + consistent Class III</td>
<td>“Possibly”</td>
</tr>
<tr>
<td>Inconsistent or &lt; 2 Class III</td>
<td>“Insufficient”</td>
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Conclusion

Riluzole is safe and effective for slowing disease progression to a modest degree in ALS (four Class I studies).
Evidence-Based Process

Question

Evidence

Conclusion

Recommendation
# Make a Recommendation

<table>
<thead>
<tr>
<th>Recommendation Level</th>
<th>Strength of Evidence</th>
<th>Value of Benefit/Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Should be offered</td>
<td>Established as</td>
<td>Large</td>
</tr>
<tr>
<td>B. Should be considered</td>
<td>Probably</td>
<td>Moderate</td>
</tr>
<tr>
<td>C. May be considered</td>
<td>Possibly</td>
<td>Small</td>
</tr>
<tr>
<td>U. No recommendation</td>
<td>Insufficient</td>
<td>Too close to call</td>
</tr>
</tbody>
</table>

- **Benefits**
- **Risks**
Recommendation

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

Robert G. Miller, MD, FAAN
Background

• In 1999, the American Academy of Neurology (AAN) published an evidence-based practice parameter for managing patients with amyotrophic lateral sclerosis (ALS).¹

• Since that publication, there have been some important new studies, including a randomized controlled trial of noninvasive ventilation (NIV) in ALS.²

• Although only one drug, riluzole, has shown modest benefit and received US Food and Drug Administration (FDA) approval, there have been advances in symptomatic treatment for patients with this disease.

• This revision updates the riluzole practice advisory and addresses other management issues for care of patients with ALS.

Gaps in Care

- As of the publication of this guideline update, only one drug, riluzole, has received FDA approval.
- The evidence for recent advances in symptomatic treatment for patients with ALS was not systematically examined before this parameter update.
- Consensus-based general principles of ALS management were developed previously to guide clinicians in managing patients with ALS.
Areas Investigated

- Drugs to slow disease progression
- Nutrition
- Respiratory management
- Multidisciplinary clinics
- Symptomatic treatment
- Telling the diagnosis and prognosis
- Cognitive and behavioral impairment
- Palliative care and end-of-life decision
Most Important Findings

- Role of multidisciplinary ALS clinics
- Riluzole: safety and modest efficacy
- Respiratory management, especially NIV
- Nutrition and the role of percutaneous endoscopic gastrostomy (PEG)
- Symptomatic treatment, especially for sialorrhea and pseudobulbar affect
- Screening for cognitive and behavioral impairment
- Telling the diagnosis, most symptoms - insufficient evidence
- Palliative care and end-of-life decisions - insufficient evidence
Analysis of Evidence, Conclusions, Recommendations

Does riluzole prolong survival or slow disease progression in ALS?

Conclusion:

- Riluzole is safe and effective for slowing disease progression to a modest degree in ALS (four Class I studies).

Recommendation:

- Riluzole should be offered to slow disease progression in patients with ALS (Level A).
What is the effect of enteral nutrition administered via PEG on weight stability?

Conclusion:

- Enteral nutrition administered via PEG is probably effective in stabilizing body weight/body mass index (two Class II, seven Class III studies).

Recommendation:

- In patients with ALS with impaired oral food intake, enteral nutrition via PEG should be considered to stabilize body weight (Level B).
Analysis of Evidence, Conclusions, Recommendations

What is the efficacy of nutritional support via PEG in prolonging survival?

Conclusion:

- Studies using appropriate controls or multivariate analysis demonstrated that PEG is probably effective in prolonging survival in ALS, although insufficient data exist to quantitate the survival advantage (two Class II studies).

Recommendation:

- PEG should be considered for prolonging survival in patients with ALS (Level B).
Nutrition Management Algorithm

Diagnosis: ALS

- Clinic visits every 3 months
- Early dysphagia detected
- Nutritional education including PEG
- Clinic visits every 3 months
- Symptom progression 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
    - Enteral nutrition via PEG as needed

FVC 30-50%
- Moderate risk
  - Anesthesia evaluation
    - Experienced gastroenterologist
  - Respiratory support during PEG if needed
  - Oral intake as tolerated

FVC < 30%
- High risk
  - PEG declined
    - Oral intake as tolerated
    - Palliative IV hydration
    - Palliative NG feeding
Analysis of Evidence, Conclusions, Recommendations

What is the efficacy of vitamin and nutritional supplements on prolonging survival in ALS?

Conclusions:

- Creatine, in doses of 5-10g daily, is established as ineffective in improving survival in ALS (two Class I studies).

- Vitamin E 5,000 mg/d plus riluzole is probably ineffective in improving survival or functional outcomes (one Class I study). Vitamin E (1,000 mg/d plus riluzole) was marginally effective in one measure of slowing ALS progression but ineffective using multiple other measures (one Class I study).
Analysis of Evidence, Conclusions, Recommendations

Vitamin and nutritional supplements

Recommendations:

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

– High-dose vitamin E should not be considered as treatment for ALS (Level B), while the equivocal evidence regarding low-dose vitamin E permits no recommendation (Level U).
Analysis of Evidence, Conclusions, Recommendations

What are the optimal pulmonary tests to detect respiratory insufficiency?

Conclusions:

- Nocturnal oximetry and maximal inspiratory pressure (MIP) are possibly more effective in detecting early respiratory insufficiency than erect forced vital capacity (FVC) (two Class III studies).

- Supine FVC is possibly more effective than erect FVC in detecting diaphragm weakness and correlates better with symptoms of nocturnal hypoventilation (two Class III studies).

- Sniff transdiaphragmatic pressure (Pdi) and sniff nasal pressure (SNP) are possibly effective in detecting hypercapnia and nocturnal hypoxemia (two Class III studies).
Analysis of Evidence, Conclusions, Recommendations

Detecting respiratory insufficiency

Recommendations:

- Nocturnal oximetry may be considered to detect hypoventilation (regardless of the FVC) (Level C).

- Supine FVC and MIP may be considered useful in routine respiratory monitoring, in addition to the erect FVC (Level C).

- SNP may be considered to detect hypercapnia and nocturnal hypoxemia (Level C).
Does NIV improve respiratory function or increase survival?

Conclusions:

– NIV is probably effective in prolonging survival (one Class I, three Class III studies).

– NIV is probably effective in slowing the rate of FVC decline (one Class I, one Class III study).

Recommendation:

– NIV should be considered to treat respiratory insufficiency in ALS, both to lengthen survival and to slow the rate of FVC decline (Level B).
AAN Practice Parameter for ALS Patient Care 2009
Respiratory Management I

Diagnosis
ALS

Symptom evaluation¹ and PFTs; Initiate NIV orientation, Pneumovax and flu vaccine

NIV Tolerated?

Consider NIV

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

NIV Tolerated?

PCEF < 270 L/min

Suction machine
Manual assisted cough
Mechanical inxsufflator
Treat sialorrhea/phlegm
How do invasive ventilation and NIV affect quality of life (QOL)?

Conclusions:

- NIV is possibly effective in raising QOL for patients with ALS who have respiratory insufficiency (five Class III studies).
- Tracheostomy invasive ventilation (TIV) is possibly effective in preserving QOL for patients with ALS, but possibly with a greater burden for their caregivers (two Class III studies).

Recommendations:

- NIV may be considered to enhance QOL in patients with ALS who have respiratory insufficiency (Level C).
- TIV may be considered to preserve QOL in patients with ALS who want long-term ventilatory support. (Level C).
AAN Practice Parameter for ALS Patient Care 2009
Respiratory Management II

NIV Tolerated?
- Yes
  - Ongoing evaluations and adjustment of pressures
  - Invasive ventilation
- No
  - Further education regarding documented benefits
  - Evaluate reasons for noncompliance
  - Reintroduce NIV
- NIV Not successful
  - Unable to maintain pO2 > 90%, pCO2 < 50mmHg or unable to manage secretions
  - Hospice referral for palliative care
- NIV Successful
  - Reintroduce NIV
  - Ongoing evaluations and adjustment of pressures
Analysis of Evidence, Conclusions, Recommendations

What factors influence acceptance of invasive ventilation and NIV?

Conclusions:

- Nocturnal oximetry is possibly effective in detecting early respiratory insufficiency and the early use of NIV possibly increases compliance (two Class III studies).
- Bulbar involvement and executive dysfunction possibly lower compliance with NIV (two Class III studies).

Recommendation:

- 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 (Level C).
Analysis of Evidence, Conclusions, Recommendations

What is the efficacy of targeted respiratory interventions for clearing secretions?

Conclusions:

- Mechanical insufflation/exsufflation (MIE) is possibly effective for clearing upper airway secretions in patients with ALS who have reduced peak cough flow, although the clinically meaningful difference is unknown (four Class III studies).

- High frequency chest wall oscillation (HFCWO) is unproven for adjunctive airway secretion management (two Class III studies with conflicting results).
Clearing secretions

Recommendations:

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

- There are insufficient data to support or refute HFCWO for clearing airway secretions in patients with ALS (Level U).

Clinical Context:

- Medications with mucolytics, nebulized saline, or an anticholinergic bronchodilator are widely used; however, no controlled studies exist in ALS.
Does multidisciplinary management improve outcomes?

Conclusions:

– Two Class II studies and one Class III study show that multidisciplinary clinics specializing in ALS care are probably effective in several ways: increased use of adaptive equipment; increased utilization of riluzole, PEG, and NIV; improved QOL; and lengthened survival. However, one Class II study with low use of treatments found no survival benefit.

Recommendations:

– Specialized multidisciplinary clinic referral should be considered for patients with ALS to optimize health care delivery (Level B) and prolong survival (Level B), and may be considered to enhance QOL (Level C).
What are the most effective treatments for sialorrhea?

**Conclusions:**

- In patients with medically refractory sialorrhea, botulinum toxin B (BTxB) injections into the parotid and submandibular glands are probably effective (one Class I study). There are inadequate data on the effectiveness of botulinum toxin A (BTxA) (one Class III study). Low-dose irradiation is possibly effective for sialorrhea (two Class III studies).

**Recommendations:**

- In patients with ALS who have medically refractory sialorrhea, BTxB should be considered (Level B) and low-dose radiation therapy to the salivary glands may be considered (Level C).
Clinical Context:

- In ALS and other diseases, anticholinergic medications are generally tried first to reduce sialorrhea, although effectiveness is unproven.\(^1\) Botulinum toxin has been effective in controlled trials in parkinsonism as well as ALS.\(^2\)

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What pharmacologic measures reduce pseudobulbar affect?

Conclusion:

- The combination of dextromethorphan/quinidine (DM/Q) is probably effective for pseudobulbar affect in ALS (one Class I study), although side effects may limit its usefulness.

Recommendation:

- If approved by the FDA, and if side effects are acceptable, DM/Q should be considered for symptoms of pseudobulbar affect in patients with ALS (Level B).
Analysis of Evidence, Conclusions, Recommendations

What pharmacologic interventions reduce fatigue?

Conclusion:

– There are no controlled studies of pharmacologic agents relieving fatigue in ALS. Riluzole may cause fatigue in some patients (two Class III studies).

Recommendation:

– In patients developing fatigue while taking riluzole, once risks of fatigue vs modest survival benefits have been discussed, withholding the drug may be considered (Level C).
Analysis of Evidence, Conclusions, Recommendations

What is the prevalence and natural history of cognitive and behavioral impairment in ALS?

Conclusion:

- A significant proportion of patients with ALS demonstrate cognitive impairment and some have dementia (two Class II, multiple Class III studies). Neither behavioral impairment in ALS nor the natural progression of cognitive or behavioral impairments have been adequately studied.

Recommendation:

- Screening for cognitive and behavioral impairment should be considered in patients with ALS (Level B).
How is cognitive or behavioral impairment in ALS diagnosed?

Conclusion:
- Neuropsychological assessment is possibly effective for identifying cognitive impairment in ALS (one Class II, one Class III).

Recommendation:
- Screening tests of executive function may be considered to detect cognitive impairment in patients with ALS prior to confirmation with formal neuropsychological evaluation (Level C).
Analysis of Evidence, Conclusions, Recommendations

The following clinical questions have only Level U evidence:

- Does lithium carbonate prolong survival or slow disease progression in ALS?
- When is PEG indicated in ALS?
- What is the effect of enteral nutrition delivered via PEG on QOL?
- How should a physician tell patients that they have ALS?
- What interventions reduce cramps?
- What interventions reduce spasticity?
- What pharmacologic interventions reduce depression?
- What pharmacologic interventions reduce anxiety?
- What pharmacologic interventions reduce insomnia?
Analysis of Evidence, Conclusions, Recommendations

Clinical questions with only Level U evidence, cont’d.:

What is the effect of cognitive or behavioral impairment on management of patients with ALS?

What treatments are effective for cognitive or behavioral impairment in ALS?

What treatments for dysarthria optimize communication in ALS?

What treatments reduce pain and dyspnea in the terminal phase of ALS?

Do hospice care, spiritual interventions, or advance directives improve QOL in the terminal phase of ALS?

What is the optimal method of withdrawing both NIV and invasive ventilation in ALS?
Lithium

- **Conclusion**: There are inadequate data on the effectiveness of lithium carbonate (one Class III study).

- **Recommendation**: There are insufficient data at this time to support or refute treatment with lithium carbonate in patients with ALS (**Level U**).

Timing of PEG placement

- **Conclusion**: There are no studies of ALS-specific indications for the timing of PEG insertion, although patients with dysphagia will possibly be exposed to less risk if PEG is placed when FVC is above 50% of predicted (one Class III study).

- **Recommendation**: There are insufficient data to support or refute specific timing of PEG insertion in patients with ALS (**Level U**).

Clinical Context

- This evidence-based review indicates some progress in evaluating new therapies for patients with ALS. More high-quality studies have been reported leading to more confident recommendations regarding the value of multidisciplinary clinics, riluzole, NIV and PEG.

- It is one thing to publish an evidence-based practice parameter for the management of patients with ALS, and it is quite another to be able to track adherence in practice and to determine whether the publication of evidence-based guidelines has changed outcomes.
Clinical Context, cont’d.

- 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 (especially PEG and NIV) has persisted in the years since the original practice parameter on this topic, though there have been gains.

Clinical Context, cont’d.

- These findings suggest that an evidence-based practice parameter 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.
Future Research

This evidence-based review indicates some progress in evaluating new therapies for patients with ALS. More high-quality studies have been reported leading to more confident recommendations regarding screening for cognitive and behavioral impairment, and symptomatic therapy for pseudobulbar effect and sialorrhea. However, future research in the following areas is still greatly needed.
Future Research, cont’d.

**Lithium carbonate**
- Study whether lithium slows disease progression or prolongs survival in ALS in larger clinical trials.

**Nutrition**
- Develop ALS-specific indications for nutritional adequacy in ALS and for PEG and radiologically inserted gastrostomy (RIG).
- Study the optimal timing of nutritional therapy administered via PEG or RIG.
- Conduct clinical studies of novel antioxidants and supplements.
Future Research, cont’d.

**Respiratory Management**

- Evaluate SNP as a criterion for NIV initiation.
- Evaluate the impact of early NIV initiation on survival and QOL.
- Assess the impact of executive dysfunction on NIV compliance.
- Evaluate the effect of hypoventilation on executive dysfunction.
- Compare techniques for clearing upper airway secretions at various stages of respiratory and bulbar dysfunction.
- Evaluate pulmonary tests, compliance with NIV, and outcomes in patients with bulbar dysfunction.
Future Research, cont.

**Breaking the News**
- Validate measures that can be applied to studies of diagnostic disclosure
- Evaluate attitudes of neurologists and patients to strategies for breaking the news
- Conduct controlled studies of the effects of different disclosure strategies on patient satisfaction, preserving hope, and outcomes

**Multidisciplinary Clinic**
- Examine referral bias to clinics
- Examine factors essential to benefits in clinics, optimal visit frequency, cost effectiveness of staff, and economic factors in care
Future Research, cont.

Symptomatic Management

- Conduct controlled trials of pharmacologic therapy for spasticity, cramps, constipation, sialorrhea, pseudobulbar affect, pain, depression, anxiety, fatigue, and therapeutic exercise
- Examine irradiation and botulinum toxin for sialorrhea in controlled trials

Cognitive and Behavioral Impairment

- Develop consensus criteria for cognitive and behavioral impairment to ensure consistency in diagnosis and research
- Identify screening tests for cognitive and behavioral impairment
- Evaluate the natural history of, and treatments for, cognitive and behavioral impairment, and their impact on compliance and survival
Future Research, cont’d.

Communication

– Validate criteria to examine communication strategies
– Design clinical trials to compare different strategies for communication in ALS

Palliative Care

– Design controlled trials of terminal symptom management, advanced directives, hospice, and spiritual care
Acknowledgments

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For a complete list of references, please access the full guidelines at www.aan.com/guidelines.