Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review)

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

ABSTRACT

**Objective:** To systematically review evidence bearing on the management of patients with amyotrophic lateral sclerosis (ALS).

**Methods:** The authors analyzed studies from 1998 to 2007 to update the 1999 practice parameter. Topics covered in this section include breaking the news, multidisciplinary clinics, symptom management, cognitive and behavioral impairment, communication, and palliative care for patients with ALS.

**Results:** The authors identified 2 Class I studies, 8 Class II studies, and 30 Class III studies in ALS, but many important areas 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:** Multidisciplinary clinic referral should be considered for managing patients with ALS to optimize health care delivery and prolong survival (Level B) and may be considered to enhance quality of life (Level C). For the treatment of refractory sialorrhea, botulinum toxin B should be considered (Level B) and low-dose radiation therapy to the salivary glands may be considered (Level C). For treatment of pseudobulbar affect, dextromethorphan and quinidine should be considered if approved by the US Food and Drug Administration (Level B). For patients who develop fatigue while taking riluzole, withholding the drug may be considered (Level C). Because many patients with ALS demonstrate cognitive impairment, which in some cases meets criteria for dementia, screening for cognitive and behavioral impairment should be considered in patients with ALS (Level B). Other management strategies all lack strong evidence.

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GLOSSARY

ALS = amyotrophic lateral sclerosis; ALS-FTD = amyotrophic lateral sclerosis with a dementia meeting the Neary criteria for frontotemporal dementia; ALSbi = amyotrophic lateral sclerosis with behavioral impairment; ALSci = amyotrophic lateral sclerosis with cognitive impairment; BTxA = botulinum toxin type A; BTxB = botulinum toxin type B; DM = dextromethorphan; FDA = Food and Drug Administration; FTD = frontotemporal dementia; NIV = noninvasive ventilation; PEG = percutaneous endoscopic gastrostomy; Q = quinidine.

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive paralyzing disease. Most patients with ALS die within 2 to 5 years of onset. The mainstay of ALS management is symptomatic treatment and palliative care. More treatments are now available to ease the burden of the disease, and they are increasingly utilized by patients and clinicians, at least in part because of the expanding base of evidence showing effectiveness. Much more needs to be done in this regard, but there has been substantial progress in the past decade.

This is part 2 of the revision of the 1999 practice parameter on the care of patients with amyotrophic lateral sclerosis (ALS).1 Consensus-based general principles of ALS management have been developed to guide clinicians in managing patients with ALS.1 Only evidence-based recommendations based on ALS studies are included in this revision.

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Appendices e1–e5, tables e1–e5, and references e1–e15 are available on the Neurology® Web site at www.neurology.org.

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DESCRIPTION OF THE ANALYTIC PROCESS
We searched OVID, MEDLINE, EMBASE, CINAHL, Science Citation Index, BIOETHICSLINE, International Pharmaceutical Abstracts, OVID Current Contents, Medline-Proquest, EIFL, and INVEST from 1998 through September 2007 combining the words ALS, Lou Gehrig’s disease, and motor neuron disease with the following words using AND: sialorrhea, pseudobulbar palsy, pseudobulbar affect, emotional lability, palliative care, diagnosis, telling the diagnosis, breaking the news, advance directives, botulinum toxin A, botulinum toxin B, parotid irradiation, anticholinergic drugs, amitriptyline, glycopyrrolate, benzphetamine, transdermal hyoscyamine, atropine, trihexyphenidyl hydrochloride, propranolol, metoprolol, dextromethorphan, quinidine, opioids, opiates, oxygen, hospice, dyspnea, pain, lorazepam, anxiety, sleep, depression, cramps, spasticity, insomnia, deep venous thrombosis, communication devices, multidisciplinary clinic, specialty clinic, cognitive impairment, dementia, fronto-temporal dementia, executive dysfunction, fatigue, and constipation. We reviewed the abstracts of these articles and examined 142 articles in their entirety. The diagnostic and therapeutic classification schemes used to grade the articles are summarized in appendices e-4a and e-4b on the Neurology® Web site at www.neurology.org. Recommendations were based on the levels of evidence as described in appendix e-5.

ANALYSIS OF EVIDENCE
Breaking the news. How should a physician tell patients that they have ALS? Telling the patient and family the diagnosis of ALS is challenging for clinicians and patients. Two studies analyzed patient perceptions of this experience (Class III and Class IV).2,3 Patients reported lack of empathy, insufficient explanation of the diagnosis and the course of the illness, and lack of information on where to get help.

Conclusion. There have been no controlled trials of breaking the news in ALS.

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

Clinical context. Useful strategies have been developed for disclosing a diagnosis of cancer (appendix e-1).4

Multidisciplinary clinic. Does multidisciplinary management improve outcomes? In specialized multidisciplinary clinics, patients with ALS receive comprehensive care from a physician, physical therapist, occupational therapist, speech pathologist, dietitian, social worker, respiratory therapist, and nurse case manager. Studies suggest varying degrees of adherence to the practice parameters (Class III).5 Specialized clinics coordinate care and interface with a primary care physician and community-based services. Patients who attend specialized ALS clinics are younger and have longer symptom duration than neurology clinic patients, indicating possible referral bias (Class II).6,9

Patient care and survival were examined for 97 patients attending specialized ALS clinics in Italy compared with 124 patients in neurology clinics (Class II).6 There was increased utilization of riluzole, percutaneous endoscopic gastrostomy (PEG), and noninvasive ventilation (NIV) in the ALS clinics, and fewer hospital admissions. Mean survival was longer in specialized ALS clinics (1,080 days vs 775 days, p = 0.008). Using the COX multivariate analysis, attending an ALS specialized clinic independently predicted longer survival.

Prolonged survival (7.5 months, p < 0.0001) was found for patients in Ireland attending multidisciplinary ALS clinics (Class II).7 Patients at ALS clinics were younger and more likely to receive riluzole (99% vs 61%). Multidisciplinary care was an independent predictor of survival (p = 0.02) and reduced the risk of death by 47% in a 5-year study (Class II).9 Dutch patients in multidisciplinary ALS clinics (n = 133) were compared with 75 patients receiving general care (Class III).10 Patients were well-matched and data were collected by a blinded nurse. Patients in multidisciplinary clinic received more aids and appliances (93.1% vs 81.3%, p = 0.008) and had higher quality of life (SF-36® Health Survey, p < 0.01). Beneficial effects derived from a single visit to a multidisciplinary clinic, suggesting better coordination of care.

By contrast, another Class II study documented no increase in survival from multidisciplinary clinic.11 Riluzole use was higher in multidisciplinary clinic (61% vs 43%, p = 0.02) but very few patients received PEG (6% vs 2%) or NIV (2% in each group). There was a nonsignificant 10% increase in survival in those attending a multidisciplinary clinic after 12 months. Low utilization of palliative care, case management, PEG, NIV, and riluzole, compared to the 2 positive studies above, may account for the lack of survival benefit in this study.

Conclusions. Two Class II studies and 1 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 quality of life; and lengthened survival. However, 1 Class II study with low use of treatments found no survival benefit.

Recommendation. 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 quality of life (Level C).

**Symptomatic management.** Effective management of symptoms is one of the primary goals of ALS patient care.

**What are the most effective treatments for sialorrhea?** Sialorrhea, or drooling, is embarrassing and is associated with aspiration pneumonia. The prevalence is estimated at 50%, and 70% of patients receiving oral medications for treatment reported benefit (Class III).12 In a small trial, amitriptyline and botulinum toxin type A (BTxA) seemed equally effective, although 3 of 5 patients treated with amitriptyline experienced side effects (Class III).13

In a double-blind, controlled trial of botulinum toxin type B (BTxB) in 20 patients with ALS with refractory sialorrhea (Class I),14 patients were randomized to 2,500 U of BTxB or placebo into bilateral parotid and submandibular glands. Treated patients reported a global improvement of 82% at 2 and 4 weeks compared to 38% in placebo ($p < 0.05$). At 12 weeks, 50% of patients receiving BTxB were improved compared to 14% receiving placebo. There were no important adverse events.

Radiation therapy for medically refractory sialorrhea reduced salivary production, but side effects included erythema, sore throat, and nausea (Class III).15 A “satisfactory response” was observed and saliva secretion rate diminished with a single dose of 7–7.5 Gy bilaterally (Class III).16

**Conclusions.** In patients with medically refractory sialorrhea, BTxB injections into the parotid and submandibular glands are probably effective (1 Class I study). There are inadequate data on the effectiveness of BTxA and amitriptyline (1 Class III study). Low-dose irradiation is possibly effective for sialorrhea (2 Class III studies).

**Recommendation.** 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.17

**What pharmacologic measures reduce pseudobulbar affect?** Pseudobulbar affect, excessive laughing or crying, or involuntary emotional expression disorder affects 20%–50% of patients with ALS, especially in pseudobulbar palsy.18 Although it is not a mood disorder, antidepressants are frequently employed.

A fixed-dose combination of dextromethorphan (DM)/quinidine (Q) (30 mg DM/30 mg Q BID) for treatment of pseudobulbar affect in ALS (Class I)19 reduced the frequency and severity of laughing and crying behaviors compared to either DM ($p < 0.001$) or Q alone ($p < 0.001$). Side effects were dizziness, nausea, and somnolence, which accounted for termination of treatment in 24% with DM/Q compared to 6% with DM and 5% with Q. DM/Q is not yet approved by the US Food and Drug Administration (FDA).

**Conclusions.** The combination of DM/Q is probably effective for pseudobulbar affect in ALS (1 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).

**What pharmacologic interventions reduce fatigue?** Fatigue may be a symptom of depression, poor sleep, abnormal muscle activation, immobility, or respiratory dysfunction. Fatigue was a side effect of therapy in 26% of patients taking riluzole vs 13% taking placebo ($p = 0.07$; number needed to harm = 8) (Class III).20 Asthenia occurred in 18% of patients taking riluzole vs 12% of patients taking placebo in a larger study ($p = 0.004$; number needed to harm = 17) (Class III).21

**Conclusions.** There are no controlled studies of pharmacologic agents relieving fatigue in ALS. Riluzole possibly causes fatigue in some patients (2 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).

**What interventions reduce cramps?** Cramps have been a secondary outcome measure in ALS clinical trials of gabapentin (Class III),22 vitamin E (Class III),23 and riluzole (Class III).20 There was no benefit from these agents.

By survey, quinine was widely used for cramps (Class IV),24 but there are no studies in ALS. Recently, the FDA warned against using quinine for cramps and removed unapproved quinine drugs from the market.25

**Conclusions.** Studies of gabapentin, vitamin E, and riluzole for treating cramps were all negative (Class III). There are safety concerns about quinine.

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

**What interventions reduce spasticity?** Treating spasticity might improve gait and relieve painful spasms. Moderate exercise led to a small decline in the Ashworth Spasticity Scale over 3 months, compared to a worsening with no exercise ($p = 0.005$) (Class III).26
Vitamin E 5,000 mg daily plus riluzole had no beneficial effect on spasticity as a secondary outcome measure (Class III).27

Conclusion. Evidence is insufficient to recommend exercise or medication for treating spasticity in ALS (Class III).

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

Clinical context. In multiple sclerosis and cerebral palsy, benzodiazepam, baclofen, dantrolene, and tizanidine are effective in reducing spasticity-related symptoms.28

What pharmacologic interventions reduce depression? The prevalence of depression in ALS ranges from 0 to 44%,29 although systematic studies suggest 10% in advanced ALS (Class III).30

Conclusion. There have been no controlled trials of treatment for depression in ALS.

Recommendation. There are insufficient data to support or refute specific treatments for depression in ALS (Level U).

Clinical context. There is consensus among experts that depression should be treated in patients with ALS31; however, there are no controlled studies of benefit or harm.

What pharmacologic interventions reduce anxiety? Recognition and treatment of anxiety in ALS can be challenging since similar symptoms can be related to dyspnea.

Conclusion. There have been no trials of treatment for anxiety in ALS.

Recommendation. There are insufficient data to support or refute specific treatment for anxiety in ALS (Level U).

What pharmacologic interventions reduce insomnia? Insomnia is common in ALS and may be a symptom of early respiratory weakness, underlying anxiety, depression, or pain.32 There is a concern that sedative/hypnotic agents may suppress the respiratory drive in patients with ALS.

Conclusion. There have been no studies of treatment for insomnia in ALS.

Recommendation. There are insufficient data to support or refute specific treatment for insomnia in ALS (Level U).

Cognitive and behavioral impairment. There is now considerable evidence for cognitive and behavioral manifestations in ALS. Specific ALS phenotypes include pure motor degeneration (ALS), ALS with cognitive impairment (ALSci), ALS with behavioral impairment (ALSbi), and ALS with a dementia meeting the Neary criteria for frontotemporal dementia (FTD) (ALS-FTD). FTD, as defined by Neary et al.,33 has insidious onset, gradual progression, altered social con-
Neuropsychological battery demonstrated 88% accuracy (Class III).37

Conclusion. Neuropsychological assessment is possibly effective for identifying cognitive impairment in ALS (1 Class II, 1 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).

What is the effect of cognitive or behavioral impairment on management of patients with ALS? In patients with ALS with frontal lobe impairment, noncompliance with PEG (72%) and NIV (75%) was greater, and survival was shorter by 11 months, compared to cognitively normal patients with ALS (Class III).e8

Conclusion. Insufficient data exist on the effect of cognitive or behavioral impairment on the management of patients with ALS.

Recommendation. There are insufficient data to support or refute the impact of cognitive and behavioral impairment on management in ALS (Level U).

What treatments are effective for cognitive or behavioral impairment in ALS? No studies were identified that evaluated pharmacologic treatment for cognitive or behavioral impairment in ALS. One Class III studye9 found an improvement in cognition after NIV initiation.

Conclusion. Data are inadequate regarding the effect of pharmacologic treatment or NIV for cognitive or behavioral impairment in ALS.

Recommendation. There are insufficient data to support or refute treatment of cognitive or behavioral impairment in ALS (Level U).

Communication. What treatments for dysarthria optimize communication in ALS? Communication is fundamental to effective participation in life, especially sharing social closeness.1 Strategies for communication with patients with ALS include an alphabet board, computerized systems, Morse code, utilization of the anal sphincter, and infrared eye movements.

Conclusion. No controlled studies examined communication in ALS.

Recommendation. There are insufficient studies examined communication in ALS (Level U).

Palliative care. Palliative care is the holistic management of symptoms in patients with terminal illness. Palliative care does not preclude active treatment or life-prolonging interventions. Hospice is a major provider of care in the final stages of ALS. Palliative care addresses advance directives and psychosocial and spiritual issues.1

What treatments reduce pain and dyspnea in the terminal phase of ALS? Pain and dyspnea are common correlates with suffering (Class IV)e10 and a desire for physician-assisted suicide in late-stage ALS (Class IV).e11

Conclusion. No controlled studies examined treating pain or dyspnea in late-stage ALS.

Recommendation. There are insufficient data to support or refute specific treatments for pain and dyspnea in late-stage ALS (Level U).

Do hospice care, spiritual interventions, or advance directives improve quality of life in the terminal phase of ALS? Systematic studies of hospice, spirituality, and advance directives in ALS are lacking.

Conclusion. No controlled studies examined hospice, spiritual care, or advance directives in ALS.

Recommendation. There are insufficient data to support or refute hospice, spiritual care, or advance directives in ALS (Level U).

What is the optimal method of withdrawing both noninvasive and invasive ventilation in ALS? Case series offer practical advice for withdrawing both invasive and noninvasive ventilation from patients with ALS (Class IV).e12,e13

Conclusion. There are no controlled studies examining withdrawal of ventilation in ALS.

Recommendation. There are insufficient data to support or refute specific strategies for withdrawal of ventilation in ALS (Level U).

Clinical context. Protocols based on consensus for withdrawal of mechanical ventilation in intensive care units (Class IV)e14 include counseling and symptom control with opioids, benzodiazepines, and anticholinergic medications.e15 We could find no controlled studies in any disease.

RECOMMENDATIONS FOR 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 multidisciplinary clinics and symptomatic therapy for pseudobulbar affect and sialorrhea. However, future research in the following areas is still greatly needed.

Breaking the news

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

Multidisciplinary clinic

1. Examine referral bias to clinics.
2. Examine factors essential to benefits in clinics, optimal visit frequency, cost effectiveness of staff, and economic factors in care.
Symptomatic management
1. Conduct controlled trials of pharmacologic therapy for spasticity, cramps, constipation, salivation, pseudobulbar affect, pain, depression, anxiety, fatigue, and therapeutic exercise.
2. Examine irradiation and botulinum toxin for salivation in controlled trials.

Cognitive and behavioral impairment
1. Develop consensus criteria for cognitive and behavioral impairment to ensure consistency in diagnosis and research.
2. Identify screening tests for cognitive and behavioral impairment.
3. Evaluate the natural history of, and treatments for, cognitive and behavioral impairment, and their impact on compliance and survival.

Communication
1. Validate criteria to examine communication strategies.
2. Design clinical trials to compare different strategies for communication in ALS.

Palliative care. Design controlled trials of terminal symptom management, advance directives, hospice, and spiritual care.

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

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