TREATMENT FOR ALS - EVIDENCE BASED MANAGEMENT

Robert G. Miller, MD
California Pacific Medical Center
San Francisco, CA

ALS is a steadily progressive disease resulting in death on average within 3 years. Approximately 20% of patients survive more than 5 years and 10% of patients more than 10 years. Although this disease is completely incurable, it is not untreatable. In fact, symptomatic treatment has advanced substantially over the last decade. In this handout, the symptomatic treatment of patients with ALS will be reviewed and the point will be made that ALS is, in fact a treatable disease[1].

Perhaps the greatest gift that an ALS clinician can give a patient is time. Spending time to remove misconceptions about the disease and educate the patient about prognosis and disease course and various therapies is time well spent. Locking arms with a patient to stare this disease straight in the face imparts courage, hope and optimism for the patient even when there is no cure.

Alternative therapies aimed at slowing a disease process are widely utilized by patients. In the ALS CARE database of North American patients with data from more than 5000 patients indicate that 85% of patients are utilizing alternative therapies at an average cost of $350.00 per month[2]. For many patients these nutritional regimens that often emphasize anti-oxidant vitamins are a source of hope in battling the disease. Unfortunately, there is no real evidence for efficacy of any of these regimens at this stage. The physician can be helpful in steering patients away from harmful or exploitative therapies and toward those which may possibly be helpful in ALS. Even though this dance with the patient is difficult, it is incredibly important not to be strongly negative or to take away all hope in this area.

Treating Symptoms

Muscle cramps, the abrupt onset of forceful and painful involuntary muscle contraction of a limb muscle group is very common in ALS. Lengthening the muscle mechanically will terminate a cramp. It is important to distinguish muscle cramp from spasticity, flexor spasms or extensor spasms, and myalgia. Partially denervated muscles are particularly prone to cramping and for some ALS patients it is a major problem. Proper diet and hydration and avoiding over-exertion of weakened muscles can all be helpful. Quinine sulfate (Quinine), lioresal (Baclofen) and gabapentin (Neurontin) may be helpful.

Muscle fasciculations are present in virtually all patients and frequently resistant to pharmacotherapy therapy. I reassure patients that they are of no pathophysiological significance and do not require drug treatment.

Spasticity is a clinical problem requiring treatment in a minority of patients with ALS. When limb stiffness results in pain or impaired mobility or difficulty with patient care, pharmacotherapy is warranted. We usually start with lioresal (Baclofen) and caution the patient that they may get sleepy as they gradually increase the dose up to a maximum of 60-80 mg/day or they may become weak as their spasticity lessens. We use tizanidine (Zanaflex) usually as a second choice and benzodiazepines (Valium, Klonapin, Ativan) or dantrolene (Dantrium) for resistant patients. A recent symptomatic review demonstrated marginal efficacy[3].

Pseudobulbar affect: Excessive laughter or crying are common in patients with pseudobulbar involvement. Usually patients do not feel sad when these outbursts of crying occur and they are difficult to control. They almost always respond to anti-depressants (see Table 1). A new combination of quinidine (Quinidex Extentabs) 60 mg/day and dextromethorphan (Benylin) 60 mg/day appears to be effective but it is still investigational[4].

Urinary urgency or frequency: Although bladder and bowel function are not involved early in most patients with ALS, urinary urgency and frequency are common when there is some upper motor neuron involvement. We generally start therapy with oxybutynin.

Sialorrhea: Excessive salivation and drooling are common in patients with bulbar and pseudobulbar abnormalities. Patients find the drooling to be not only inconvenient but socially very embarrassing. We often start with glycopyrrolate (Pyridium) or amitriptyline (Elavil). A scopolamine patch is often helpful. Most patients will become refractory to pharmacotherapy orally over time. Botulinium toxin (Botox) injection is an option which is helpful for

the majority of patients. We have only rarely employed focal irradiation. For patients who have very thick phlegm and post nasal drip, we usually use guaifenesin (Robitussin, Humibid).

Laryngospasm: Laryngospasm is a sudden onset of closure of the vocal cords resulting in wheezing and apnea. These attacks are common in patients with ALS and often precipitate a panic reaction which aggravates the attack. Triggering factors include smoke, alcohol, spicy foods, sinus drainage and gastric reflux. The attacks usually resolve spontaneously in less than a minute and strong reassurance for patients about the benign character of the attacks is often sufficient treatment. H_1 and H_2 blockers may be helpful in selected patients. Benzodiazepines (Valium, Klonapin, Ativan) are sometimes needed in very anxious patients.

Insomnia: Insomnia is very common in patients with ALS as is early morning wakening. Many of these patients are depressed (see below). Since fatigue is such a common problem in ALS and since these patients often have a disturbed sleep pattern, restoring a nourishing sleep can be a big help in combating fatigue. A disturbed sleep pattern should also make the clinician become suspicious about respiratory insufficiency since with early weakness of the respiratory musculature, abnormalities during sleep may lead to hypoxemia. Nasal mechanical ventilation may effectively treat these symptoms[5,6] (see page 5). Nocturnal oximetry or a polysomnogram should be ordered when respiratory insufficiency is suspected to search for nocturnal hypoxemia and/or sleep apnea. We usually use tricyclic antidepressant such as amitriptyline (Elavil) for insomnia.

Depression and Anxiety: Depression and anxiety are extremely common in this patient population. Studies have indicated the incidence of depression as between 25% and 50% of patients affected. The diagnosis of depression is often missed because of the magnitude of the pressing physical problems and the expectation that patients will be depressed. Depression has a negative impact on patient quality of life and possibly also upon survival[7,8]. Effective therapy for depression is often extremely gratifying for patient and physician. We usually start with the selective serotonin re-uptake inhibitors. When patients are agitated and anxious, we tend to use a calming medication such as: sertraline (Zoloft), citalopram (Celexa) or escitalopram (Lexapro). When patients are in need of activation from psychomotor retardation, we usually use fluoxetine (Prozac), venlafaxine (Effexor), bupropion (Welbutrin), or mirtazapine (Remeron).

Pain: Although most patients with ALS do not experience pain in the early phases of the disease, more than 50% of patients ultimately experience pain. Major sources of pain include pressure and traction on tendons and ligaments in weak muscles. Cramps, spasticity and spasms all contribute. Evidence-based recommendations include non-steroidal anti-inflammatory medication or aspirin, acetaminophen (Tylenol) or propoxyphene (Darvon). When these medications become ineffective, opioids should be utilized to treat pain[1,9].

Constipation: Constipation is an extremely common problem in patients with ALS. The combination of reduced activity and progressive motor neuron dropout as well as the use of pain medications all contribute to constipation. Adequate hydration and diet are all important. “Power Pudding”, equal parts of prunes, prune juice, apple sauce and bran, starting with two tablespoons with each meal and at bedtime is often effective. Increasing fruits and vegetables in the diet, stool softeners, laxatives and periodic enemas should all be used as needed.

Terminal Symptoms: Other treatments for patients in the final phases of life are extremely important. Most patients develop dyspnea, agitation, anxiety and air hunger in the final phase of ALS. Liberal use of opioids, benzodiazepines ((Valium, Klonapin, Ativan) is now the standard of care. This topic is dealt with in detail (see below).

Slowing Disease Progression

Riluzole

One of the most plausible hypotheses for ALS pathogenesis is the excess glutamate that causes excitotoxic damage to motor neurons. Riluzole is an anti-glutamate agent that inhibits the presymptomatic release of glutamate. In two placebo-controlled, double blind clinical trials, riluzole was shown to have a modest beneficial impact in ALS[10,11]. In both trials, there was an increase in survival, but this averaged only 2-3 mos. The first trial showed mild slowing in deterioration of muscle strength compared to the placebo group, but the second study did not confirm this treatment effect. Neither study showed improvement in quality of life[12-15].

A post-hoc analysis of the same data showed slight prolongation in the time it took patients on riluzole to move from milder to more severe health states[11], but the effect was not apparent to patients, family members, or physicians[16]. Two recent reports of patients on long-term riluzole suggest that survival may be extended further, but the validity of these observational studies has been questioned[17-20]. Another recent report suggested that

high blood levels may be associated with longer survival, although these data are not conclusive[21]. High levels are also accompanied by diarrhea. In the future, dose adjustment based on blood level may be a more acceptable way to treat patients with riluzole, although blood levels are not widely available.

Another important source of evidence-based neurology is the Cochrane Library, consisting of systematic reviews of randomized controlled trials (Class I evidence). A Cochrane review pertaining to treatment of patients with ALS/MND was recently published[22]. Four randomized controlled trials have been conducted examining efficacy and safety of riluzole in patients with ALS, but the study in Japan involved different outcome measures and could not be included in a meta-analysis. The other three published studies[10,11,17] have been analyzed in detail in the Cochrane Review[22] and in a recent report from the National Institute of Clinical Effectiveness (NICE) in the UK[23]. The three trials examining tracheostomy-free survival included a total of 876 riluzole treated patients and 406 placebo treated patients. Riluzole 100 mg per day appears to be very modestly effective and safe in prolonging survival, by approximately 2 months, for patients with ALS.

Side effects

Riluzole is safe and well tolerated with few patients complaining of nausea and fatigue. More than threefold elevation of serum transaminases was rare. Recent studies show large inter-individual variability in serum concentration of riluzole (70%) probably on the basis of fast and slow metabolizers[24]. Side effects tend to be more frequent in those with high serum levels. The long-term safety of riluzole therapy has also been established[25,26], including use by elderly patients and those in advanced stages of the disease[27].

Utilization of riluzole

A survey of 559 ALS patients from 10 medical centers was conducted in 1996 after the Food and Drug Administration (FDA) approved the use of riluzole for the treatment of ALS[28]. Only 43% of ALS patients had taken the drug even though 90% knew about it. Patients identified factors that had a major effect on their decision to start riluzole: small benefit of the drug (45%); expense (31%); opinion of ALS physician (23%); risk of side effects (14%); and opinions of family/friends (10%). 63% of patients who took riluzole paid less than $25/month while 12% paid more than $600/month. 34% discontinued the drug due to either lack of benefit, expense or adverse effects. The probability of taking riluzole ranged from 18-75% at different centers. Independent risk factors that significantly influenced the probability of taking riluzole included whether the ALS physician encouraged (odds ratio 6.8) or discouraged (odds ratio 0.1) the patient from taking riluzole, as well as Medicare coverage (providing no pharmaceutical benefit; odds ratio 0.6).

Since the majority of patients who took riluzole had insurance that paid most of the cost, the decision to use riluzole was determined in large part by fiscal issues. Recent ALS CARE database analyses indicate that 59% of patients with ALS take riluzole at present, a number that has slowly risen[29,30].

Evidence-Based Treatment

Most of the symptomatic treatment recommended above is based on personal experience and anecdotes. Many treatment strategies in medicine are based upon lessons learned in training, personal opinion, recent articles or "curbside consults", with colleagues or experts. As a result, there is a substantial variation in treatment practices between different physicians and also between tertiary care centers. This is true in ALS management as well as in general medical treatment. One egregious example of this high degree of variance is the pattern of utilization of non-invasive mechanical ventilation (NPPV) for patients with respiratory insufficiency. In one large North American study, utilization of NPPV ranged from 0 – 50% of patients in different centers[31].

Evidence-based medicine provides a firm basis for decision-making in managing patients with ALS/MND[32]. In the evidence-based medicine process, all pertinent studies are analyzed, the evidence examined and recommendations are formulated to guide clinical decision-making. The resultant systematic review is based on a statistical analysis of all available studies and differs substantially from most narrative reviews, which are not evidence-based.

Recently, the American Academy of Neurology sponsored an evidence-based review of management strategies for patients with ALS/MND[9]. The purpose of the systematic review was to improve the standard of care and the quality of life of patients with ALS.

A multi-disciplinary task force working with a methodologist and research librarian identified 5350 abstracts and 750 relevant articles that met pre-determined inclusion criteria. The details of the literature search, a more complete description of the process and a more detailed summary of the evidence are described elsewhere[3].

The following principles of managing patients with ALS were agreed upon:
1) Respect for patient autonomy;
2) The importance of informing patients in their cultural and psychosocial context;
3) Attention to appropriate timing for decision-making, which may change over time.
4) The importance of providing the full continuum of care from diagnosis through palliative care in the terminal phase.

The classification scheme, which is used to grade the strength of evidence, is contained in Table 2. The strength of recommendations is described in Table 3. There was no class I evidence to guide management in ALS and therefore none of the recommendations could be classed as Standards. Class II evidence was available and many of the recommendations were classified as Guidelines while some with lower strength evidence were classified as Options.

The guidelines were focused upon five areas:
1) Informing patients about the diagnosis and prognosis;
2) Treatment of symptoms (sialorrhea and pseudobulbar affect);
3) Decision-making about percutaneous endoscopic gastrostomy (PEG);
4) Managing respiratory insufficiency; and
5) Palliative care.

The last three will be discussed here.

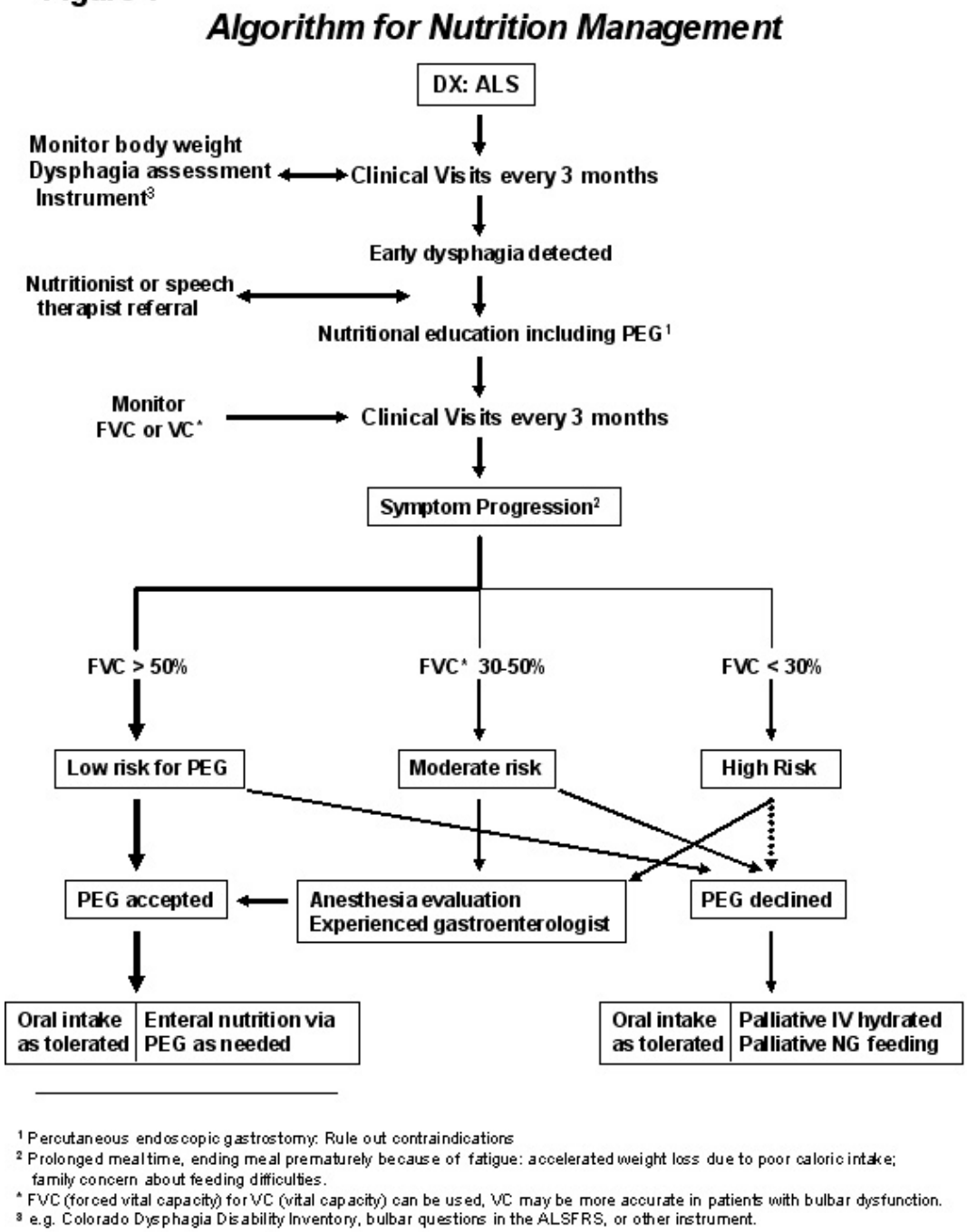
Informing the patient

Much of the evidence on informing patients about the diagnosis (Breaking the News) comes from studies in patients with cancer. The information should be shared with patients and families in quiet surroundings, in person by the attending physician, and in a way that takes into consideration the cultural background of the patient. The other major principle in breaking the news is to avoid taking away hope from patients and families. Several positive points are often very reassuring to patients. First, more than 20% of patients survive longer than 5 years and more than 10% of patients with ALS survive more than 10 years. Recovery has been documented in rare cases. Second, symptomatic treatments are available which provide substantial relief from some of the major problems engendered by ALS. Third, the first drug riluzole, which slows the disease process, has been approved in the United States and in many European countries. Fourth, the momentum of neuroscience research pertinent to ALS/MND is accelerating, including exciting advances in the laboratory involving stem cells, gene therapy, growth factors and promising new pharmacologic agents.

Nutrition

Patients with symptomatic dysphagia should be informed about PEG (Fig 1). Evidence indicates that patients with PEG have prolonged survival compared with patients who do not have PEG. Indications for PEG include: progressive weight loss, fatigue and prolonged time for eating a meal, choking during feeding and difficulty swallowing medication. Evidence indicates that the risk of PEG placement increases with declining respiratory function[9]. In patients with low vital capacity, the radiologic guided insertion of a gastrostomy is a viable option[33].

Figure 1



[1] Percutaneous endoscopic gastrostomy. Rule out contraindications
[2] Prolonged meal time, ending meal prematurely because of fatigue: accelerated weight loss due to poor caloric intake; family concern about feeding difficulties.
[*] FVC (forced vital capacity) for VC (vital capacity) can be used, VC may be more accurate in patients with bulbar dysfunction.
[3] e.g. Colorado Dysphagia Disability Inventory, bulbar questions in the ALSFRS, or other instrument.

Recommendations:

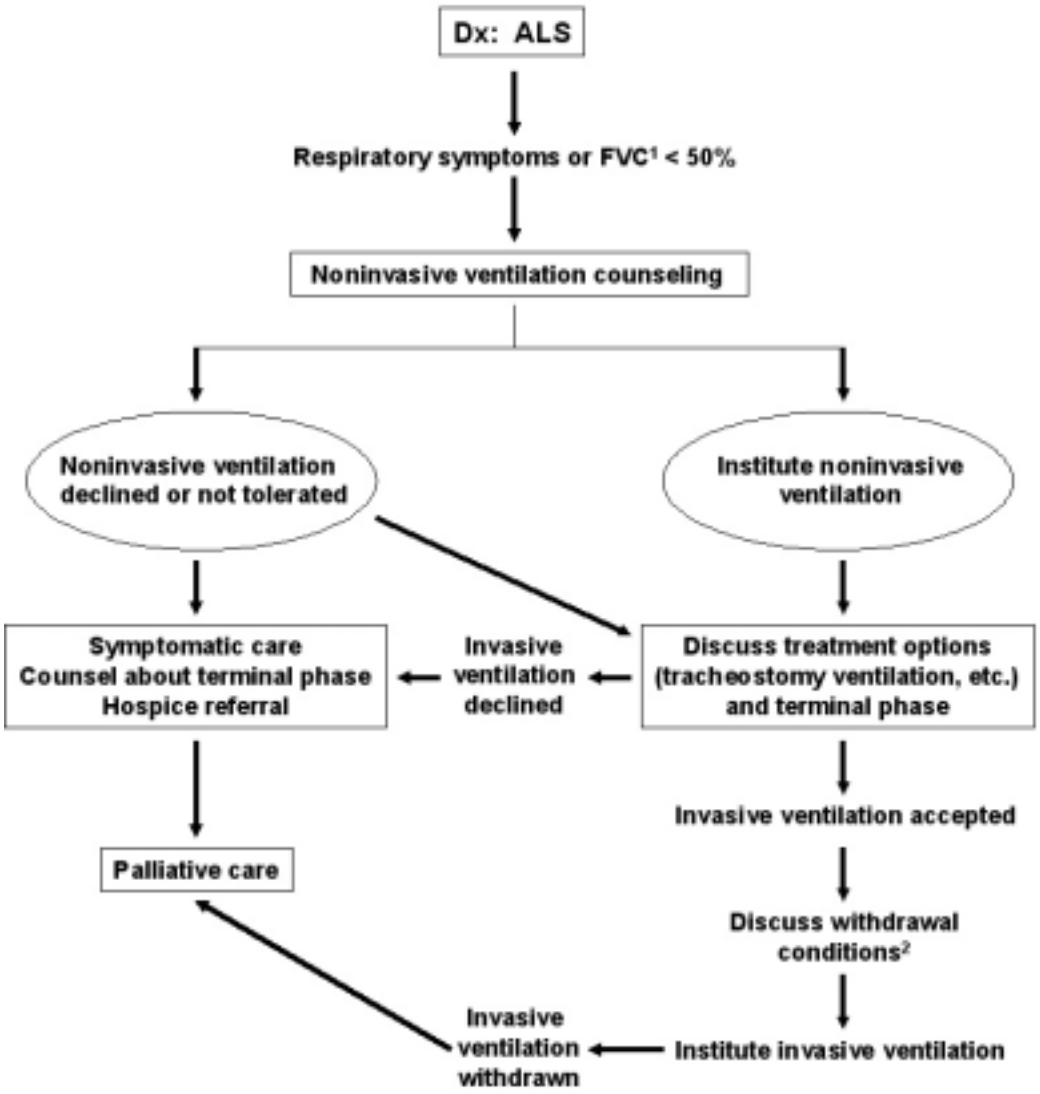
1. PEG is indicated for patients with symptomatic dysphagia and should be placed soon after symptom onset (Guideline).
2. For optimal safety and efficacy, PEG should be placed when vital capacity is more than 50% of predicted (Guideline).

Respiratory Management

Most patients with ALS die from complications of respiratory insufficiency. Thus, the management of respiratory problems is critical (Fig 2). The Task Force formulated four clinical questions that play a critical role in respiratory management for patients with ALS: 1) What is the best test of early respiratory insufficiency? 2) Does non-invasive positive pressure ventilation improve hypoventilation and lengthen survival? 3) Does mechanical ventilation improve quality of life? and 4) What is the optimal method of withdrawing mechanical ventilation?

Figure 2

Algorithm for Respiratory Management



[1]FVC (forced vital capacity) or VC (vital capacity) can be used. VC may be more accurate in patients with bulbar dysfunction.
[2]Agreement needed for conditions of withdrawal, prior to, or concurrent with, instituting invasive ventilation (e.g. locked instate, coma, etc.)

The evidence indicates that there is no single best test of pulmonary function to detect early signs of respiratory insufficiency[34]. Moreover, early symptoms of respiratory insufficiency are subtle and easily overlooked if not specifically searched for. When vital capacity falls to 50%, respiratory symptoms are often present and planning decisions should be made. Evidence indicates that NPPV is effective treatment for hypoventilation and improves quality of life. Studies have documented prolonged survival in patients with ALS treated with NPPV[5,6,12,34-37] including impressive survival and QoL benefits in a recent randomized trial[38]. Invasive (with tracheostomy) ventilation may more effectively prolong survival but with a greater financial and care burden. When initiating mechanical ventilation, it is critical to determine under what circumstances a patient wishes to withdraw from mechanical ventilation since communication will eventually be compromised in all patients with ALS. This contract between patient and physician should be arranged at the time of instituting mechanical ventilation or soon thereafter. Finally, evidence indicates that adequate treatment with opioids, oxygen and anxiolytics should be provided when withdrawing mechanical ventilation.

Recommendations:

1. Be vigilant for symptoms indicating hypoventilation. Serial measures of pulmonary function (especially vital capacity) are recommended to guide management and determine prognosis with the understanding that no single test can reliably detect hypoventilation. (Guideline)
2. Offer noninvasive ventilatory support as an effective initial therapy for symptomatic chronic hypoventilation, and to prolong survival in patients with ALS. (Guideline)
3. When long-term survival is the goal, offer invasive ventilation and fully inform patient and family of burdens and benefits. (Guideline)
4. In accordance with the principle of patient autonomy, physicians should respect the right of the patient with ALS to refuse or withdraw any treatment, including mechanical ventilation. (Guideline)
5. When withdrawing ventilation, use adequate opiates, and anxiolytics to relieve dyspnea and anxiety. (Guideline)

Bioethics Statement: It is a strong consensus of both the ALS Task Force and the Quality Standards Subcommittee of the AAN that during withdrawal of ventilation, paralyzing drugs should not be used.

Palliative Care

Palliative care begins after the diagnosis of ALS[39]. All management efforts should be directed toward improving comfort and quality of life for patients with ALS. For clues about when to discuss end of life care, and what to cover see Tables 4 & 5 respectively[39,40]. When patients enter the advanced stages of the disease, evidence indicates that up to 50% of patients develop pain from immobility, ligamentous laxity etc. Pain should be treated assertively beginning with non-narcotic analgesics and using opioids if necessary in doses sufficient to alleviate pain.

Dyspnea is a common complaint for patients in the late stages of the disease. Although oxygen is generally not indicated in earlier stages of the disease, dyspnea in the terminal stages of the disease responds to opioids with or without oxygen and anxiolytics[9].

Recommendations:

<u>For pain management</u>

1. Utilize non-narcotic analgesics, anti-inflammatory drugs, and anti-spasticity agents for initial treatment of pain in patients with ALS. (Option).
2. Administer opioids liberally, following the WHO guidelines, when non-narcotic analgesics fail (Option).

<u>For treating dyspnea in terminal stages of ALS</u>

1. Use opioids, alone or with supplemental oxygen to treat dyspnea at rest in patients with ALS, despite the risk of respiratory depression with higher doses (Option).
2. Consider chlorpromazine (Thorazine) and acupuncture as possible adjuncts (Option).

<u>For hospice care</u>

1. Consider referral to hospice in the terminal phase of ALS. (Option).

<u>For Advance Directives:</u>

1. Initiate a discussion of advance directives well in advance of the terminal phase and re-evaluate at least every six months. (Option)

Dissemination and Implementation of Evidence-based Practice Guidelines

Publication of evidence-based guidelines is often not enough to change physician behavior. Some physicians are not aware of the guidelines; others may not agree with some of the guidelines, third party payor policies and limited fiscal resources may limit implementation. Finally, studies to determine whether guidelines have improved the quality of patient care are needed to complete the quality improvement process.

In North America, a large database involving more than 5,000 patients with ALS is designed to evaluate patient management and clinical outcomes[41].
This voluntary database is open to all clinicians who see patients with ALS. Clinicians who wish to participate can do so by following instructions on the ALS C.A.R.E. website (http://www.umassmed.edu/outcomes/als/index.cfmoffice).

At the time of publication of the ALS Practice Parameters in April 1999, only a small percentage of patients were receiving PEG and non-invasive positive pressure ventilation in accord with the practice parameters[42]. By

contrast a substantial majority of patients died peacefully without choking, air hunger or fear. Follow up studies have shown definite improvement in the utility of life-prolonging therapies such as PEG and BiPAP. PEG use increased from 12% of patients to 19% of patients between 1996 and 2002 after the introduction of the practice parameter. Patients who were receiving BiPAP increased from 9% to 14% in the North American ALS CARE database. More than 90% of patients were judged to have died peacefully by their caregivers, although 20% of patients had breathing difficulty near the time of death and 4% had anxiety or fear while 3% had some difficulty with choking.

These data indicate some progress in utilizing various therapies for patients with ALS but still indicate an opportunity for substantial improvement in improving quality of life and prolonging life for patients with ALS using these therapies[42].

Quality of Life in ALS

Quality of life is difficult to measure in any disease and this is certainly true in ALS[43]. Many instruments designed to measure quality of life place great emphasis upon the physical domain without clear focus upon existential concerns such as purpose, meaning of life and capacity for personal growth. Such instruments as the sickness impact profile (SIP) and an abbreviated version called the SIP-ALS 19 have been found to correlate with strength measurements and indicate a heavy emphasis upon physical function[44,45]. Recent studies utilizing the McGill quality of life questionnaire, which includes an existential domain, examine the relationship between physical function and quality of life and also the relationship of spiritual and religious factors to quality of life. The results indicated a close correlation of the overall quality of life score with multiple psychological and existential subscores of the McGill instrument but poor correlations with the SIP-ALS 19. This study suggested that quality of life for the patient with ALS depends more upon psychological and existential concerns than physical functioning[46]. A study of the individual quality of life – direct weighting (SEIQoL-DW) indicated that quality of life scores correlated with the existence of confiding and emotional support and they were inversely correlated with the presence of cognitive difficulty[47]. In this study physical impairment and functional limitations did not correlate closely with quality of life.

There have been relatively few studies of quality of life and communication among patients on long-term tracheostomy (invasive) positive pressure ventilation (TPPV). Patients may survive from 5-18 years using TPPV as documented in a recent study of 70 patients[48]. Surprisingly, many patients retain the ability to communicate at least to some degree. Of patients on TPPV for more than five years, 18% became totally locked in and unable to communicate and 33% had the ability to communicate in a minimal fashion primarily with eye movements. This study documents the very long survival that is possible for patients with ALS using TPPV. It also highlights the important dilemma about communication. New methods to improve communication are under development which may help with these issues in the future. Patients must be educated about these issues with respect to developing a contract about when they would wish the ventilation to be discontinued.

Studies of caregivers and patients have shown some differences with respect to quality of life matters. In a group of patients and caregivers where there were no significant differences between quality of life and depression scores, caregivers tended to underestimate the patient's quality of life by a substantial degree. Attitudes about future BiPAP were also very different with only 3% of patients being opposed compared to 32% of caregivers[49]. These data suggest that both education and help should be offered to both patients and caregivers[50]. Another study examined fatigue and depression in patients' with poor quality of life and ALS. Fatigue, depression and excessive daytime sleepiness were all more pronounced in patients compared to controls[47]. Both fatigue and depression correlated with poorer quality of life in patients and should be treated aggressively. Studies have differed in reports of the incidence of depression in patients with ALS varying from 18% up to 50%[7,8].

Further studies examining the level of patient suffering in patients with ALS have provided important insights. In a recent study of 100 patients, it was found that many patients with pain and depression did not receive adequate treatment[51]. Quantitative measures of patient perceived suffering were closely correlated with increased pain, hopelessness as well as the level of physical disability. Poor quality of life was found in patients who had insufficient social support and increasing levels of hopelessness. There was a good correlation between the perception of the caregiver and that of the patient in rating the patient's suffering[51]. Thus, suffering appears to have both physical and social as well as psychological correlates. These findings indicate an opportunity for treatment of patients with ALS who have pain and hopelessness (which is often secondary to depression). Unfortunately, recent studies indicate that both pain and depression are under-treated in patients with ALS[2,52], although there has been substantial improvement over the past four years[30,53].

Studies have shown that spirituality or religiousness influence patient coping skills as well as decision-making about both PEG and also nasal mechanical ventilation in ALS. In one study, patients who were more spiritual were less likely to select a PEG but those who were more religious were more likely to opt for nasal mechanical ventilation[54]. Patients who were more religious appeared to have better coping skills in accepting major transitions of the disease, including the process of dying.

End of life issues will be reviewed by Dr. Wendy Johnston

REFERENCES:

1. Gelinas DF, Miller RG. A treatable disease: a guide to the management of amyotrophic lateral sclerosis. In: R.H. Brown Jr, V. Meininger, M. Swash (eds) Amyotrophic Lateral Sclerosis (chapter 23): 405-421.

2. Bradley WG, Anderson F, Bromberg M, Gutmann L, Harati Y, Ross M, Miller RG, and the ALS C.A.R.E. Study Group. Current Management of ALS: Comparison of the ALS CARE Database and the AAN Practice Parameter. Neurology 2001; 57:500-504.

3. Montanė E, Vallano A, Laporte JR. Oral antispastic drugs in nonprogressive neurologic diseases: A systemic review. Neurology 2004;63:1357-1363.

4. Brooks BR, Thisted, RA Appel SH, Bradley WG, Olney RK, Berg JE, Pope LE, Smith RA for the AVP-923 ALS Study Group. Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: A randomized trial. Neurology 2004;63:1364-1370.

5. Lyall RA, Donaldson N, Fleming T, et al. A prospective study of quality of life in ALS patients treated with noninvasive ventilation. Neurology 2001;57:153–156.

6. Pinto A. de Carvalho M. Evangelista T. Lopes A. Sales-Luis L. Nocturnal pulse oximetry: a new approach to establish the appropriate time for non-invasive ventilation in ALS patients. ALS & Other Motor Neuron Disords. 2003; 4:31-35.

7. Lou JS. Reeves A. Benice T. Sexton G. Fatigue and depression are associated with poor quality of life in ALS. Neurology 2003; 60:122-123.

8. Iwasaki Y, Iguchi H, Ichikawa Y, Igarashi O, Kawabe S, Lou J-S, et al. Fatigue and depression are associated with poor quality of life in ALS. Neurology 2003;61:872.

9. Miller RG, Rosenberg JA, Gelinas DF et al. and the ALS Practice Parameters Task Force. Practice Parameter: The care of the patient with amyotrophic lateral sclerosis (an evidence-based review). Report of the Quality Standards Subcommittee of the AAN. Neurology 1999; 52:1311-1323.

10. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. N Engl J Med 1994;330:585-591.

11. Lacomblez L, Bensimon G, Leigh PN, et al. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. Lancet 1996;347:1425-1431.

12. Rowland LP. Riluzole for the treatment of amyotrophic lateral sclerosis--too soon to tell? N Engl J Med 1994;330:636-637.

13. Rowland LP and Shneider NA. Medical Progress: Amyotrophic lateral sclerosis. N Engl J Med 2001;344:1688-1700.

14. Riviere M, Meininger V, Zeisser P and Munsat TL. An analysis of extended survival in amyotrophic lateral sclerosis patients treated with riluzole. Arch Neurol 1998;55:526-8.

15. Sojk P, Anderson PM, Forsgren L. Effect of riluzole on symptom progression in amyotrophic lateral sclerosis. Lancet 1997;349:176-7.

16. Anonymous. Practice advisory on the treatment of amyotrophic lateral sclerosis with riluzole: report of the Quality Standards Subcommittee of the American Academy of Neurol. Neurology 1997;49:657-659.

17. Meininger V, Dib M, Aubin F, et al. The Riluzole Early Access Programme: descriptive analysis of 844 patients in France. ALS/Riluzole Study Group III. J Neurol 1997;244 Suppl 2:S22-25.

18. Hugon J. Riluzole and ALS therapy. Wiener Medizinische Wochenschrift 1996;46:185-187.

19. Traynor BJ, Alexander M, Corr B et al. Riluzole and prognosis in ALS: findings of the Irish ALS registry from 1995-2000. ALS & other Motor Neuron Disords 2001;2 (Suppl 2):43-4.

20. Brooks BR, Belden DS, Roelke K et al. Survival in non-riluzole-treated ALS/MND patients with disease onset before and since 1996 is identical: A clinic based epidemiologic study. ALS & Other Motor Neuron Disords 2001;2(Suppl 2):60-1.

21. Groeneveld GJ, Van Kan HJ, Kalmijn S, Veldink JH, Guchelaar HJ, Wokke JH, Van Den Berg LH. Riluzole serum concentrations in patients with ALS: Associations with side effects and symptoms. Neurology. 2003 Oct 28;61(8):1141-1143.

22. Miller, R., Mitchell, J. and Moore, D. Riluzole for amyotrophic lateral sclerosis/motor neuron disease (Cochrane Review). Cochrane Library, Oxford. 2005.

23. National Institute for Clinical Excellence (NICE). Guidance on the use of riluzole (Rilutek) for the treatment of motor neurone disease. Technology Appraisal Guidance - No. 20, 2001.

24. Miller RG, Bouchard JP, Duquette P, et al. Clinical trials of riluzole in patients with ALS. ALS/Riluzole Study Group-II. Neurology 1996;47(Suppl 2):S86-90; discussion S90-82.

25. Debove C, Zeisser P, Salzman PM, Powe LK, Truffinet P: The Rilutek (riluzole) Global Early Access Programme: an open-label safety evaluation in the treatment of amyotrophic lateral sclerosis. ALS & Other Motor Neuron Disords 2001;2:153-8.

26. Lacomblez L, Bensimon G, Leigh PN, Debove C, Bejuit R, Truffinet P, Meininger V: Long-term safety of riluzole in amyotrophic lateral sclerosis. ALS & Other Motor Neuron Disords 2002;3:23-9.

27. Bensimon G, Lacomblez L, Delumeau JC, Bejuit R, Truffinet P, Meininger V: A study of riluzole in the treatment of advanced stage or elderly patients with amyotrophic lateral sclerosis. J Neurol 2002;249:609-15.

28. Bryan WW, McIntire D, Camperlengo L et al. Factors influencing the use of riluzole by ALS patients. 8th International Symposium on ALS/MND. November 1997 (abstract).

29. Miller RG, Mitsumoto H, Brooks BR, Gowda N, Anderson F, for the ALS CARE Group. Temporal Trends in the Treatment of ALS in North America: Findings from the ALS CARE Patient Database. ALS & Motor Neuron Disords 2004;2:42.

30. Bradley WG, Anderson F, Gowda N, Miller RG and the ALS CARE Study Group. Improvement in the management of ALS since 1999 publication of AAN Practice Parameter: Evidence from the ALS patient CARE database. ALS & Other Motor Neuron Disords 2003;4(suppl1):21-22.

31. The BDNF Study Group. Phase III trial of subcutaneous recombinant methionyl human BDNF in patients with ALS. Neurology 1999; 52:1427-1433.

32. Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based Medicine: How to practice and teach EBM. Edinburgh, Scotland: Churchill & Livingstone, 1997.

33. Thornton FJ. Fotheringham T. Alexander M. Hardiman O. McGrath FP. Lee MJ. Amyotrophic lateral sclerosis: enteral nutrition provision--endoscopic or radiologic gastrostomy? Radiology 2002;224:713-717.

34. Lechtzin N, Rothstein J, Clawson L, Diette GB, Wiener CM. Amyotrophic lateral sclerosis: evaluation and treatment of respiratory impairment. ALS & Other Motor Neuron Disords 2002;3:5–13.

35. Butz M. Wollinsky KH. Wiedemuth-Catrinescu U. Sperfeld A. Winter S. Mehrkens HH. Ludolph AC. Schreiber H. Longitudinal effects of noninvasive positive-pressure ventilation in patients with amyotrophic lateral sclerosis. Amer J Phys Med & Rehab 2003; 82:597-604.

36. Lechtzin N, Anderson FA, Brooks BR, Gowda NJ, Miller RG, Mitsumoto H, Moore D. Non-Invasive Positive Pressure Ventilation Use and Outcomes in Patients with Amyotrophic Lateral Sclerosis. ALS & Other Motor Neuron Disords. 2004;5(suppl 2):57.

37. Bourke SC, Bullock RE, Williams TL, Shaw PJ, Gibson GJ. Noninvasive Ventilation in ALS. Neurology 2003;61:171-177.

38. Bourke SC, Tomlinson M, Williams TL, Shaw PJ, Bullock RE, Gibson GJ. Randomised Controlled Trial of Non-Invasive Ventilation in Amyotrophic Lateral Sclerosis. ALS & Other Motor Neuron Disords. 2004;5(suppl 2):59.

39. Quill TE. Initiating End of Life Discussions with seriously ill patients: Addressing the “Elephant in the Room”. JAMA 2000; 284:2502-2507.

40. Oliver D, Borasio GD, Walsh D. Palliative Care in Amyotrophic Lateral Sclerosis: Oxford University Press Inc, New York. 2000.

41. Miller RG, Anderson FA, Bradley WG, et al. and the ALS C.A.R.E. Study Group. The ALS Patient Care Database: Goals, design, and early results. Neurology 2000; 54:53-57.

42. Bradley WG, Lessard D, Miller RG et al. Discrepancies between Recent Management Practices in ALS and the AAN Evidence-Based Practice Parameters as revealed by the ALS Patient Care Database. Neurology 2000;54:A341.

43. Bromberg MB, Dallas A. Forshew DA. Comparison of instruments addressing quality of life in patients with ALS and their caregivers. Neurology 2002;58:320 - 322.

44. McGuire D, Garrison L, Miller RG: Relationship of the Tufts Quantitative Neuromuscular Exam (TQNE) and the Sickness Impact Profile (SIP) in measuring progression of ALS. Neurology 1996; 46:1442-1444.

45. McGuire D, Garrison, L, Armon C, Barohn RJ, Bryan WW, Miller RG, Parry GJ, Petajan JH, Ross MA and The Syntex-Synergen ALS/CNTF Study Group. A brief quality-of-life measure for ALS clinical trials based on a subset of items from the Sickness Impact Profile. J. Neurol Sci 1997; 152(suppl. 1):S18-22.

46. Simmons Z, Bremer BA, Robbins RA, Walsh SM, Fischer S. Quality of life in ALS depends on factors other than strength and physical function. Neurology 2000; 55:388-392.

47. Goldstein LH. Atkins L. Leigh PN. Correlates of Quality of Life in people with motor neuron disease (MND). ALS & Other Motor Neuron Disords. 2002;3:123-129.

48. Hayashi H, Oppenheimer EA. ALS patients on TPPV: Totally locked-in state, neurologic findings and ethical implications. Neurology, 2003; 61:135-137.

49. Trail M. Nelson ND. Van JN. Appel SH. Lai EC. A study comparing patients with amyotrophic lateral sclerosis and their caregivers on measures of quality of life, depression, and their attitudes toward treatment options. J Neurol Sci. 2003; 209:79-85.

50. Nelson ND. Trail M. Van JN. Appel SH. Lai EC. Quality of life in patients with amyotrophic lateral sclerosis: perceptions, coping resources, and illness characteristics. J Palliat Med 2003;6:417-424.

51. Ganzini L, Johnston WS, Hoffman WF. Correlates of suffering in amyotrophic lateral sclerosis. Neurology 1999; 52:1434-1440.

52. Mandler RN, Anderson FA, Miller RG, Clawson L, Cudkowicz, Del Bene M and the ALS C.A.R.E. study group. The ALS Patient Care Database: Insights into End-of-Life Care in ALS. ALS & Other Motor Neuron disords 2001; 2:203-208.

53. Mitsumoto H, Anderson FA, Albert S, Gowda NJ, Miller RG, Rosenfeld J, Strong M, Bromberg M. Improving End of Life Care in ALS: Findings from the ALS Patient CARE Database. ALS & Other Motor Neuron Disords 2004;5:43.

54. Murphy PL, Albert SM, Weber CM, Del Bene MS, Rowland LP. Impact of spirituality and religiousness on outcomes in patients with ALS. Neurology 2000; 55:1581-1584.

TABLE 1 – Commonly used medications for symptomatic ALS Treatment

Symptoms	**Medication**
Muscle cramps and spasms	lioresal (Baclofen) tizanidine (Zanaflex) quinine sulfate (Quinine)
Spasticity (stiffness of limbs)	lioresal (Baclofen) tizanidine (Zanaflex) benzodiazepines (Valium)
Excessive crying or laughter	Tricyclic antidepressants (Amitriptyline) Selective serotonin reuptake inhibitors (Lexapro, Celexa, Zoloft, Prozac) valproate (Depakote) lithium (Lithobid)
Urinary urgency or frequency	Oxybutynin (Ditropan)
Excessive saliva	Tricyclic antidepressants (Amitriptyline) glycopyrrolate (Pyridium) scopolamine (Scopace) botulinium toxin injection (Botox)
Thick phlegm or post nasal drip	guaifenesin (Robitussin, Humibid) nebulizer treatments
Laryngospasm (throat closing sensation)	benzodiazopines (Valium, Klonapin, Ativan)
Insomnia	Tricyclic antidepressants (Trazodone) zolpidem (Ambien) temazepam (Restoril)
Depression/anxiety	Selective serotonin reuptake inhibitors (Prozac, Paxil, Zoloft, Celexa, Lexapro) venlafaxjne (Effexor) buproprion (Welbutrin) mirtazepine (Remeron)
Pain	nonsteroidal anti-inflammatory (Motrin, Celebrex, Vioxx) pain medicine (Tylenol, darvon) aspirin narcotics (Vicodin, morphine, oxycontin)
Nausea	prochloperazine (Compazine)
Constipation	stool softeners (Colace) laxatives (Senekot, Ducolax) fiber (Metamucil) enemas

TABLE 2 – Definitions of Classification of Evidence

Class I:	Evidence provided by one or more well-designed, randomized, controlled clinical trials
Class II:	Evidence provided by a cohort study with controls, either prospective but not randomized, or retrospective case control series
Class III:	Uncontrolled, nonrandomized reports
	a) evidence provided by uncontrolled observational series (IIIa)
	b) case reports (IIIb)
	c) topic reviews (IIIc)

TABLE 3 – Classification of Management Recommendations

Standard:	A principle for patient management that reflects a high degree of certainty based on Class I evidence, or very strong evidence from Class II studies when circumstances preclude randomized trials.
Guideline:	Recommendations for patient management reflecting moderate clinical certainty (usually Class II evidence or strong consensus of Class III evidence).
Option:	A strategy for patient management for which the evidence (Class III) is inconclusive or where there is some conflicting evidence or opinion.

TABLE 4 – *Clinical Indications for Discussing End-of-Life Care*[4]

Urgent Indications
Imminent death
Talk about wanting to die
Inquiries about hospice or palliative care
Recently hospitalized for severe progressive illness
Severe suffering and poor prognosis
Routine Indications
Discussing prognosis
Discussing treatment with low probability of success
Discussing hopes and fears
Physician would not be surprised if the patient died in 6-12 months.

TABLE 5 – *What to include in most End-of-Life Discussions*[4]

General: Goals of Treatment
Relative emphasis on life prolongation
Relative emphasis on quality of life
Routine Indications
Advance directives
Living will
Healthcare proxy
Do not (attempt) resuscitation (DNR) orders
Other life-sustaining therapies, such as:
Mechanical ventilation
Feeding tube
Antibiotics
Hemodialysis
Palliative Care
Management of pain and other symptoms
Relieve of psychological, social, spiritual and existential suffering
Creating opportunity to address unfinished business

Treating Symptoms in ALS – Evidence Based Management

Robert G. Miller, M.D.
Department of Neurosciences
California Pacific Medical Center
San Francisco, CA

Treatable Symptoms of ALS

1. **Psychological disturbances**
2. **Sleep disturbance**
3. **Fatigue**
4. **Pain**
5. **Dyspnea**
6. **Weight loss**
7. **Constipation**
8. **Drooling**
9. **Spastic**
10. **Cramps**
11. **Emotionality**

Medication for Cramps

- **Quinine sulfate** **200 mg bid**
- **Carbamazepine** **200 mg bid**
- **Phenytoin** **100 mg qd tid**
- **Magnesium** **5 mmol qd tid**
- **Vitamin E** **400 IU bid**

Medications for Spasticity

- **Baclofen** **10-80 mg**
- **Tizanidine** **6-24 mg**
- **Memantine** **10-60 mg**
- **Dantrolene** **50-300 mg**

Montané et al, 2004

Medication for pathologic laughing/crying

Amitriptyline	10-150 mg
Fluvoxamine	100-200 mg
Lithium carbonate	400-800 mg
L-Dopa	500-600 mg
Quinidine	60 mg
Dextromethorphan	60 mg

Sedatives

Amitriptyline	25-100 mg
Chloral Hydrate	500 mg
Diphenhydramine	250-1000 mg
Lorazepam	0.5-2.5 mg

Medication for Drooling

- **Glycopyrrolate** **0.1-0.2 mg sc/im tid**
- **Amitriptyline** **10-150 mg**
- **Transdermal hyoscine patches** **1-2 patches**
- **Atropine/benztropine** **0.25-0.75 mg/1-2 mg**
- **Trihexyphenidyl** **6-10 mg**
- **Clonidine** **0.15-0.3 mg**

*Source of Pain in 42 patients with ALS**

Source of Pain	*n (%)*
Muscle Cramps	23 (55)
Aching, low back/legs	14 (33)
Falls/trauma	10 (24)
Aching, shoulder/neck	6 (14)
Leg pain	6 (14)
Headaches	6 (14)
Gastrostomy tube site	2 (5)
Decubitus ulcer	1 (2)
Arthritis	1 (2)

*Some subjects had pain in more than one site, hence total percentage >100

Ganzini et al Neurology, 2002

Symptoms of Chronic Respiratory Insufficiency

- Daytime fatigue and sleepiness, concentration problems
- Difficulty falling asleep, disturbed sleep, nightmares
- Tachypnea, dyspnea, phonation difficulties
- Reduced appetite, weight loss, morning headache
- Recurrent or chronic upper respiratory tract infections
- Cyanosis, edema, tachycardia, use of auxiliary respiratory muscles

NPPV & QoL in ALS

- 16 pts - sleep disordered resp (PSG)
- Decreased daytime sleepiness ($p<0.0001$)
- Increased vitality ($p=0.001$)

Lyall, 2001

NPPV Benefits in ALS

- Orthopnia predicted NPPV use
- Improved daytime sleepiness
- Improved QoL, survival (RCT 2004)
- Slower decline of VC
- Less use/improvement bulbar

Bourke 2003, 2004

Improving HRQOL in ALS

Oncologists - 64% med/tech, 23% HRQOL
Patients - 41% med/tech, 48% HRQOL

Neglecting Serious HRQOL

- Emotional Function - 54%
- Fatigue - 48%
- Daily Activities - 37%
- Pain - 20%

Delmar JAMA, 2001

Fatigue and Depression in ALS

- Increased fatigue (general, physical, *NOT* motivation or mental)
- 44% depressed (11/25)
- Psychological well-being (WB) correlated with physical WB (r=0.42), existential WB (r=0.68) and support (r=0.53) (MQOL)
- Disease severity (ALSFRS, MRC) not correlated to QOL, fatigue or depression

Recommend: SSRI, amantadine, modafinil

Lou et al, 2003

Riluzole

- AAN Practice Advisory - Neurology 1997
- Approved in Canada 2000 (U.S., Europe 1996)
- National Institute for Clinical Effectiveness (NICE)
  - Systematic review 4 trials
  - Approved in U.K. (2001)
  - Cochrane Review 2003
- Registry Data (UK, IR, UW) - 8-16m increased survival

Implications for Practice

- Proven efficacy - modest effect size
- Generally safe and well tolerated
- Expensive ($10,000 US/yr)
- Provides hope - none before
- Education - adjustment/perception

Irish Experience

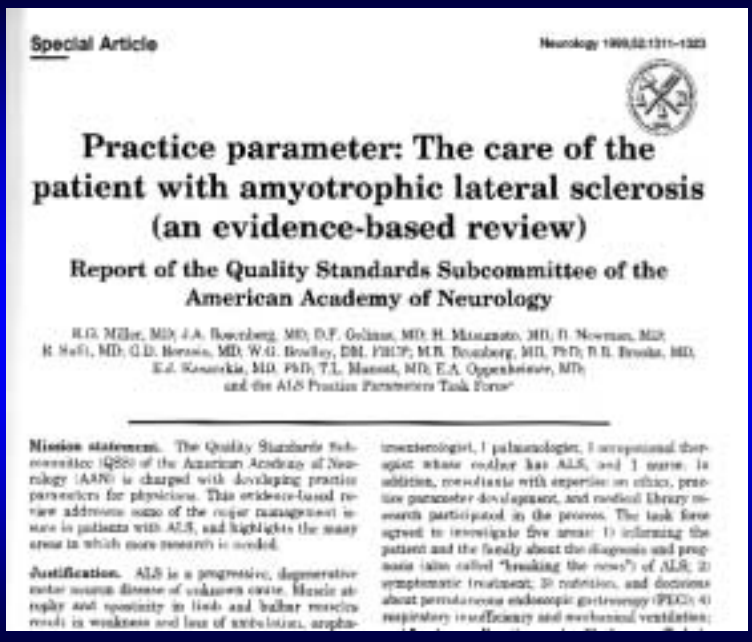
- ALS Clinic advantages
  - More riluzole use (99% vs. 61%)
  - Longer survival (7 mos, $p<0.0001$)
- Riluzole survival longer (4 mos)

Traynor, 2003

Riluzole Use

- **Modest benefit (45%)**
- **Cost (31%)**
- **MD Opinion (23%)**
- **Side Effects (14%)**
- **Opinion - friends/family (10%)**

Bryan, 1997



Special Article

Neurology 1999;52:1311–1323

Practice parameter: 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

R.G. Miller, MD; J.A. Rosenberg, MD; D.F. Gelinas, MD; H. Mitsumoto, MD; D. Newman, MD; R. Stefl, MD; G.D. Bornais, MD; W.G. Bradley, DM, FRCP; M.B. Bromberg, MD, PhD; D.B. Brooks, MD; E.J. Kasarskis, MD, PhD; T.L. Munsat, MD; E.A. Oppenheimer, MD; and the ALS Practice Parameters Task Force*

Mission statement. The Quality Standards Subcommittee (QSS) of the American Academy of Neurology (AAN) is charged with developing practice parameters for physicians. This evidence-based review addresses some of the major management issues in patients with ALS, and highlights the many areas in which more research is needed.

Justification. ALS is a progressive, degenerative motor neuron disease of unknown cause. Muscle atrophy and spasticity in limb and bulbar muscles result in weakness and loss of ambulation, amputa-

neurologist, 1 pulmonologist, 1 occupational therapist whose mother has ALS, and 1 nurse. In addition, consultants with expertise in ethics, practice parameter development, and medical library research participated in the process. The task force agreed to investigate five areas: 1) informing the patient and the family about the diagnosis and prognosis (also called "breaking the news") of ALS; 2) symptomatic treatment; 3) nutrition, and decisions about percutaneous endoscopic gastrostomy (PEG); 4) respiratory insufficiency and mechanical ventilation;

ALS Practice Parameter

- Developed by a task force assembled by AAN's Quality Standards Subcommittee
- Published April 1999
- Based on evidence-supported medicine
- Purpose is to improve standard of care and quality of life of people with ALS by providing rational basis for managing ALS

AAN Practice Parameter for ALS Patient Care

Nutrition

- Recommendations
  - Percutaneous endoscopic gastrostomy (PEG) is indicated for patients with symptomatic dysphagia soon after symptom onset (Guideline)
  - For optimal safety and efficacy, PEG should be offered and placed when the VC is more than 50% of predicted (Guideline)
  - With low FVC, consider radiologic guided gastrostomy. (*Thornton et al , 2002*)

61 yr old woman with ALS

- Dysphagia, dysarthria 6 mos; limbs normal
- Weight loss 15% bw, (166 to 142 pounds)
- Choking rare, enjoys meals
- Vital capacity 55%; adv directive no life support
- Decision: Wait, PEG or RIG?

AAN Practice Parameter for ALS Patient Care

Respiratory Management

- Recommendations
  - Offer noninvasive ventilatory support as an effective initial therapy for symptomatic chronic hypoventilation, and to prolong survival in patients with ALS (Guideline)
  - When long-term survival is the goal, offer invasive ventilation and fully inform patient and family of burdens and benefits (Guideline)

- 56F – bulbar onset ALS – orthopnea
- FVC 75%
- MIP 30 cm H_20, $p0_2$=78, pCO_2=42
- Nocturnal desaturation < 90, 4 min
- HCFA: FVC<50%, $pC0_2$>45, desat<90/5m, MIP<60

AAN Practice Parameter for ALS Patient Care

Palliative Care

- Recommendations for Pain Management
  - Administer opioids liberally, (WHO guidelines), when non-narcotic analgesics fail (Guideline).
- Recommendations for Terminal Dyspnea
  - Use opioids, alone or with supplemental oxygen, despite the risk of respiratory depression with higher doses (Guideline)

AAN Practice Parameter for ALS Patient Care

Palliative Care

- Recommendations for Hospice Care
  - Consider referral to hospice in the terminal phase of ALS (Option)
- Recommendations for Advance Directives
  - Initiate discussion of advance directives well in advance of the terminal phase; re-evaluate at least every six months (Option)

ALS Patient Care Database: Overview

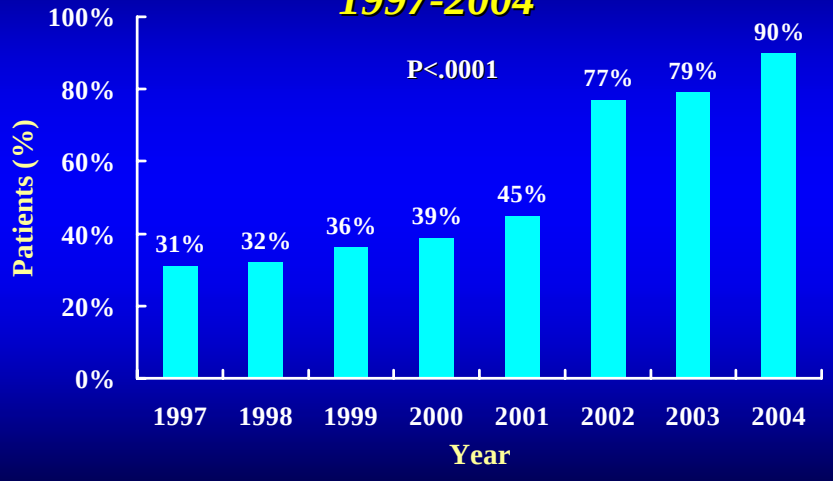
- Part of ALS Clinical Assessment, Research, and Education (C.A.R.E.) Program
- Voluntary, confidential, outcomes-based database
- Mechanism for evaluating impact of diagnostic and therapeutic decisions
- Foundation for assessing current patterns of clinical practice

Discrepancies Between Recent Management Practice in ALS and the AAN ALS Practice Parameter, as revealed by the ALS Patient Care Database

Bradley WG, Lessard D, Singleton C, Anderson F, Bromberg M, Gutmann L, Harati Y, Ross M, Miller R and the ALS CARE Study Group

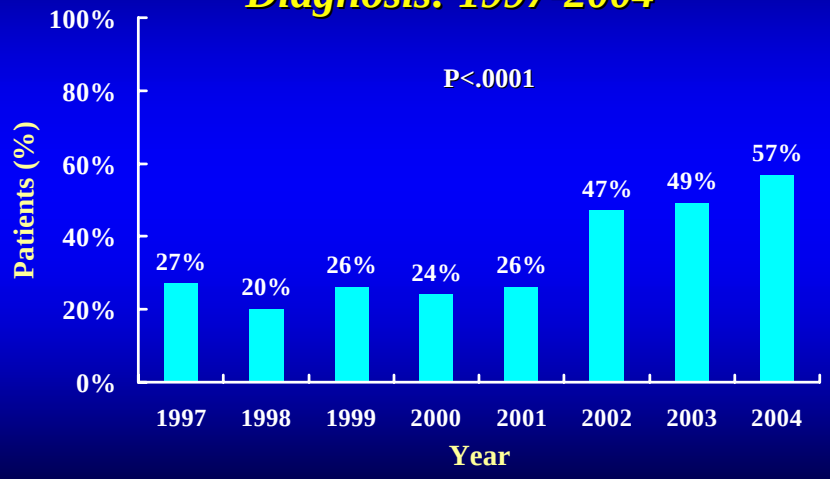
Neurology, 2003

Temporal Trends in Medication for Depression Over 6 Months after Diagnosis: 1997-2004



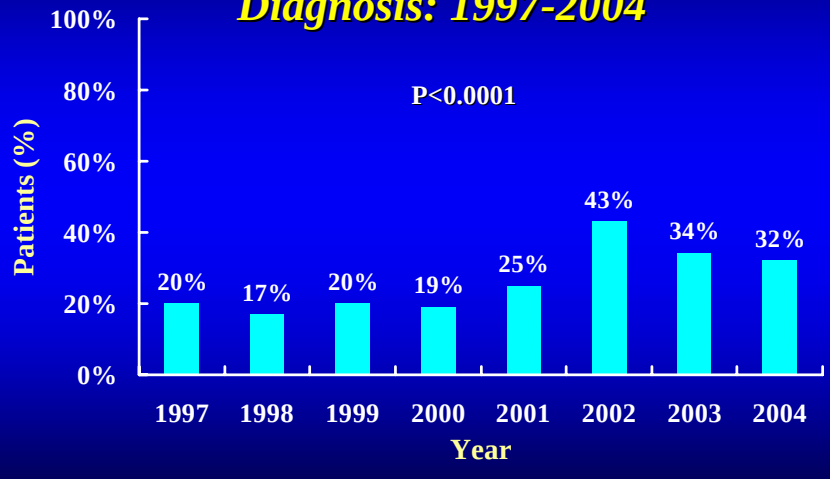
August 31, 2004

Temporal Trends in Medication for Sleep Disturbance Over 6 Months after Diagnosis: 1997-2004



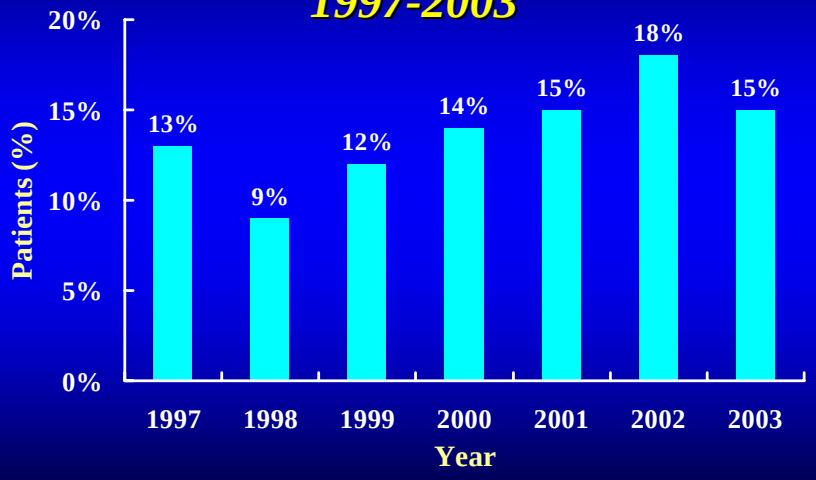
August 31, 2004

Temporal Trends in Use of Nutritional Supplements Over 6 Months after Diagnosis: 1997-2004



August 31, 2004

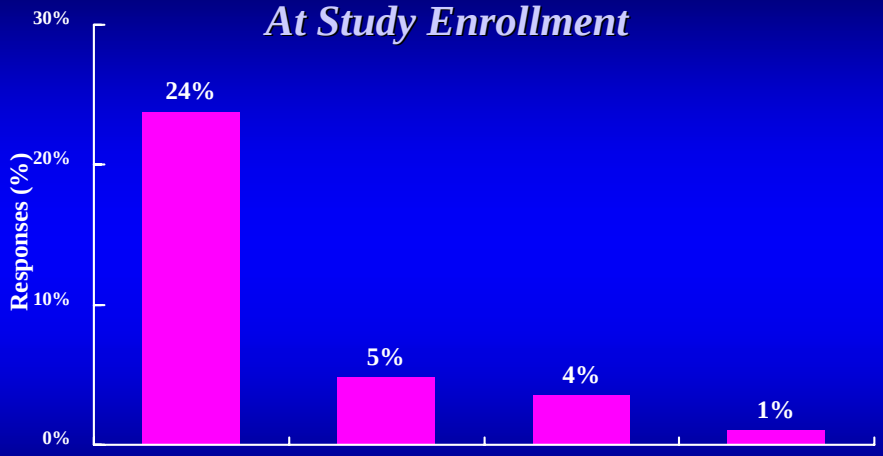
Temporal Trends in Feeding Modalities Over 6 Months after Diagnosis: 1997-2003



August 31, 2004

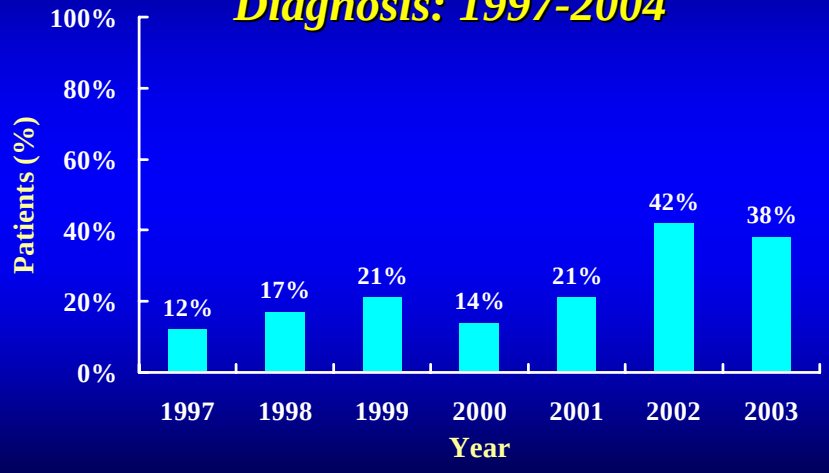
Reasons for Not Using PEG

At Study Enrollment



August 31, 2003

Temporal Trends in Respiratory Interventions Over 6 Months after Diagnosis: 1997-2004



August 31, 2004

Summary

- Database allows monitoring of adherence to Practice Parameter
- Aspects of practice that appear to have improved
  - Number of patients treated for marked sialorrhea and pseudobulbar affect
  - Use of PEG in appropriate patients
- As more data from new forms becomes available there will be opportunities to monitor adherence to additional aspects of Parameter