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.

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. 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 dantrelene (Dantrium) for resistant patients. A recent symptomatic review demonstrated marginal efficacy.

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 (Quinindex Extentabs) 60 mg/day and dextromethorphan (Benylin) 60 mg/day appears to be effective but it is still investigational.

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 (Wellbutrin), 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\textsuperscript{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\textsuperscript{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\textsuperscript{10,11,17} have been analyzed in detail in the Cochrane Review\textsuperscript{22} and in a recent report from the National Institute of Clinical Effectiveness (NICE) in the UK\textsuperscript{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\textsuperscript{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\textsuperscript{25,26}, including use by elderly patients and those in advanced stages of the disease\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{31}.

Evidence-based medicine provides a firm basis for decision-making in managing patients with ALS/MND\textsuperscript{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\textsuperscript{33}. 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\textsuperscript{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. In patients with low vital capacity, the radiologic guided insertion of a gastrostomy is a viable option.
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?
The evidence indicates that there is no single best test of pulmonary function to detect early signs of respiratory insufficiency\textsuperscript{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\textsuperscript{5,6,12,34-37} including impressive survival and QoL benefits in a recent randomized trial\textsuperscript{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. 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. 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.

Recommendations:
For pain management
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).

For treating dyspnea in terminal stages of ALS
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).

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

For Advance Directives:
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. 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.

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. 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.

**Quality of Life in ALS**

Quality of life is difficult to measure in any disease and this is certainly true in ALS. 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. 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. 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. 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. 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. These data suggest that both education and help should be offered to both patients and caregivers. 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. 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%.

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. 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. 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, although there has been substantial improvement over the past four years.
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\textsuperscript{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:


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.


**TABLE 1 – Commonly used medications for symptomatic ALS Treatment**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Medication</th>
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<tbody>
<tr>
<td>Muscle cramps and spasms</td>
<td>lioresal (Baclofen)</td>
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<tr>
<td></td>
<td>tizanidine (Zanaflex)</td>
</tr>
<tr>
<td></td>
<td>quinine sulfate (Quinine)</td>
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<tr>
<td>Spasticity (stiffness of limbs)</td>
<td>lioresal (Baclofen)</td>
</tr>
<tr>
<td></td>
<td>tizanidine (Zanaflex)</td>
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<tr>
<td></td>
<td>benzodiazepines (Valium)</td>
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<tr>
<td>Excessive crying or laughter</td>
<td>Tricyclic antidepressants (Amitriptyline)</td>
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<tr>
<td></td>
<td>Selective serotonin reuptake inhibitors (Lexapro, Celexa, Zoloft, Prozac)</td>
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<tr>
<td></td>
<td>valproate (Depakote)</td>
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<td></td>
<td>lithium (Lithobid)</td>
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<tr>
<td>Urinary urgency or frequency</td>
<td>Oxybutynin (Ditropan)</td>
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<tr>
<td>Excessive saliva</td>
<td>Tricyclic antidepressants (Amitriptyline)</td>
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<td></td>
<td>glycocyprrolate (Pyridium)</td>
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<td></td>
<td>scopolamine (Scopace)</td>
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<td></td>
<td>botulinum toxin injection (Botox)</td>
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<td>Thick phlegm or post nasal drip</td>
<td>guaifenesin (Robitussin, Humibid)</td>
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<tr>
<td></td>
<td>nebulizer treatments</td>
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<tr>
<td>Laryngospasm (throat closing sensation)</td>
<td>benzodiazepines (Valium, Klonapin, Ativan)</td>
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<tr>
<td>Insomnia</td>
<td>Tricyclic antidepressants (Trazodone)</td>
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<td>zolpidem (Ambien)</td>
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<tr>
<td></td>
<td>temazepam (Restoril)</td>
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<tr>
<td>Depression/anxiety</td>
<td>Selective serotonin reuptake inhibitors (Prozac, Paxil, Zoloft, Celexa, Lexapro)</td>
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<td></td>
<td>venlafaxine (Effexor)</td>
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<td>buproprion (Wellbutrin)</td>
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<td></td>
<td>mirtazepine (Remeron)</td>
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<td>Pain</td>
<td>nonsteroidal anti-inflammatory (Motrin, Celebrex, Vioxx)</td>
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<td>pain medicine (Tylenol, darvon)</td>
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<td>aspirin</td>
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<tr>
<td></td>
<td>narcotics (Vicodin, morphine, oxycontin)</td>
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<tr>
<td>Nausea</td>
<td>prochlorperazine (Compazine)</td>
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<td>Constipation</td>
<td>stool softeners (Colace)</td>
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<tr>
<td></td>
<td>laxatives (Senekot, Ducolax)</td>
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<td></td>
<td>fiber (Metamucil)</td>
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<td>enemas</td>
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### TABLE 2 – Definitions of Classification of Evidence

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

### TABLE 3 – Classification of Management Recommendations

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Standard</td>
<td>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.</td>
</tr>
<tr>
<td>Guideline</td>
<td>Recommendations for patient management reflecting moderate clinical certainty (usually Class II evidence or strong consensus of Class III evidence).</td>
</tr>
<tr>
<td>Option</td>
<td>A strategy for patient management for which the evidence (Class III) is inconclusive or where there is some conflicting evidence or opinion.</td>
</tr>
</tbody>
</table>

### TABLE 4 – Clinical Indications for Discussing End-of-Life Care

<table>
<thead>
<tr>
<th>Indications</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgent Indications</td>
<td>Imminent death&lt;br&gt;Talk about wanting to die&lt;br&gt;Inquiries about hospice or palliative care&lt;br&gt;Recently hospitalized for severe progressive illness&lt;br&gt;Severe suffering and poor prognosis</td>
</tr>
<tr>
<td>Routine Indications</td>
<td>Discussing prognosis&lt;br&gt;Discussing treatment with low probability of success&lt;br&gt;Discussing hopes and fears&lt;br&gt;Physician would not be surprised if the patient died in 6-12 months.</td>
</tr>
</tbody>
</table>

### TABLE 5 – What to include in most End-of-Life Discussions

<table>
<thead>
<tr>
<th>Indications</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>General: Goals of Treatment</td>
<td>Relative emphasis on life prolongation&lt;br&gt;Relative emphasis on quality of life</td>
</tr>
<tr>
<td>Routine Indications</td>
<td>Advance directives&lt;br&gt;Living will&lt;br&gt;Healthcare proxy&lt;br&gt;Do not (attempt) resuscitation (DNR) orders&lt;br&gt;Other life-sustaining therapies, such as:&lt;br&gt;  - Mechanical ventilation&lt;br&gt;  - Feeding tube&lt;br&gt;  - Antibiotics&lt;br&gt;  - Hemodialysis&lt;br&gt;Palliative Care&lt;br&gt;  - Management of pain and other symptoms&lt;br&gt;  - Relieve of psychological, social, spiritual and existential suffering&lt;br&gt;  - Creating opportunity to address unfinished business</td>
</tr>
</tbody>
</table>
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*

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

*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*

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**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

---

**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

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

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. Motor atrophy and spasticity in limbs and bulbar movements result in weakness and loss of autonomy, dysphagia, dysarthria, and frequent respiratory embarrassment. It is associated with significant physical, psychological, and social alteration.
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 H₂O, pO₂=78, pCO₂=42
- Nocturnal desaturation < 90, 4 min
- HCFA: FVC<50%, pCO₂>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)

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**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


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

Patients (%)

Year
August 31, 2004

P<.0001

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

Patients (%)

Year
August 31, 2004

P<0.0001
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

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