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EFNS TASK FORCE/CME ARTICLE

EFNS task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives

An evidence-based review with good practice points

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Despite being one of the most devastating diseases known, there is little evidence for diagnosing and managing patients with amyotrophic lateral sclerosis (ALS). Although specific therapy is lacking, correct early diagnosis and introduction of symptomatic and specific therapy can have a profound influence on the care and quality of life of the patient and may increase survival time. This document addresses the optimal clinical approach to ALS. The final literature search was performed in the spring of 2005. Consensus recommendations are given graded according to the EFNS guidance regulations. Where there was lack of evidence but consensus was clear we have stated our opinion as good practice points. People affected with possible ALS should be examined as soon as possible by an experienced neurologist. Early diagnosis should be pursued and a number of investigations should be performed with high priority. The patient should be informed of the diagnosis by a consultant with a good knowledge of the patient and the disease. Following diagnosis, the patient and relatives should receive regular support from a multidisciplinary care team. Medication with riluzole should be initiated as early as possible. PEG is associated with improved nutrition and should be inserted early. The operation is hazardous in patients with vital capacity $< 50\%$. Non-invasive positive pressure ventilation improves survival and quality of life but is underused. Maintaining the patients ability to communicate is essential. During the entire course of the disease, every effort should be made to maintain patient autonomy. Advance directives for palliative end of life care are important and should be fully discussed early with the patient and relatives respecting the patients social and cultural background.

Introduction

Amyotrophic lateral sclerosis (ALS, also known as motor neuron disease (MND), sclérose latérale amyotrophique (SLA) is a fatal syndrome characterized by onset of symptoms and signs of degeneration of primarily upper (UMN) and lower (LMN) motor neurons, leading to progressive weakness of bulbar, limb, thoracic and abdominal muscles. Other brain functions, including oculomotor and sphincter functions, are relatively spared, although these may be involved in some cases. Cognitive dysfunction is seen in 20–50%, and 3–5% develop dementia that is usually of frontotemporal type (Abrahams *et al*., 1996). Death due to respiratory failure follows on average 2–4 years after onset, but a small group may survive for a decade or more (Forsgren *et al*., 1983). The mean age of onset is 47–52 years in familial cases (FALS) and 58–63 years in sporadic (SALS) cases (Haverkamp *et al*., 1995). The lifetime risk of developing ALS is about 1:1000 [approximately half the risk of getting

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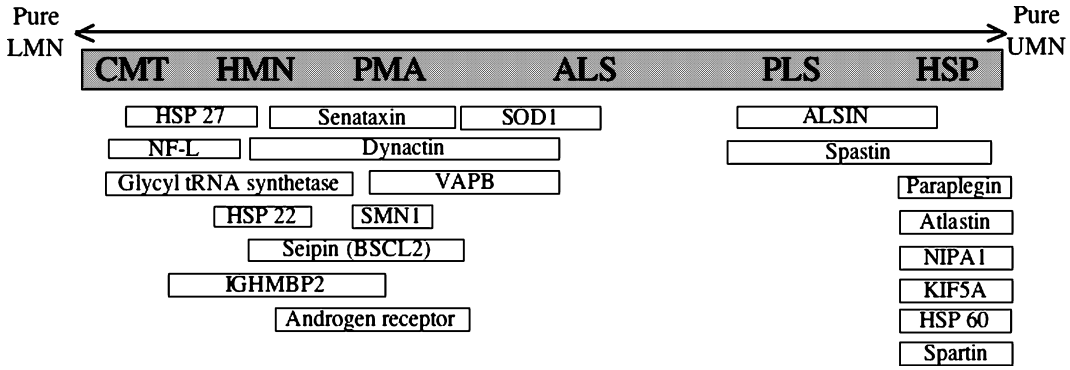

Figure 1 Schematic illustration of the relationship between ALS and some other motor neuron syndromes and motor neuronopathies. On the far left are syndromes affecting lower motor neurons (LMN) and/or the peripheral motor axons, on the right syndromes affecting the upper motor neurons and/or the corticospinal and corticobulbar tractsystems. The approximate clinical spectrum associated with mutations in some genes is shown below the bar. At present, 44 genes have been associated with motor neuron disease or neuronopathy. CMT, Charcot-Marie-Tooth; HMN, distal hereditary motor neuronopathies; PMA, progressive spinal muscular atrophies; PLS, primary lateral sclerosis syndrome; HSP, hereditary spastic paraplegias.

multiple sclerosis], with male sex, increasing age and hereditary disposition being the main risk factors (Bobowick and Brody, 1973). When diagnosing and managing a patient with ALS it is important to recognize that ALS is a heterogeneous syndrome that overlaps with a number of other conditions (Fig. 1; Ince *et al.*, 1998; Brugman *et al.*, 2005). This systematic review comprises of an objective appraisal of the evidence in regard to the diagnosis and clinical management of patients with ALS. The primary aim has been to establish evidence-based and patient and carer centered guidelines, with secondary aims of identifying areas where further research is needed.

Methods

Two investigators screened potentially relevant citations independently. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library to date); MEDLINE-OVID (January 1966 to date); MEDLINE-ProQuest; MEDLINE-EIFL; EMBASE-OVID (January 1990 to date); Science Citation Index (ISI); The National Research Register; Oxford Centre for Evidenced-based Medicine; American Speech Language Hearing Association (ASHA); the world Federation of Neurology ALS Page of reviews of published research; the Oxford Textbook of Palliative Medicine, and the UK Department of Health National Research Register (http://www.update-software.com/National/). We also searched national neurological databases (e.g. http://www.alsa.org and http://www.alsod.org) and personal collections of references and reference lists of articles. There were no constraints based on language or publication status. Any differences at any stage of the review were resolved by discussion.

Results

Ten central issues in the management of ALS were addressed by the Task Force. The following is an abbreviated report, the full report with all tables, figures and references is available at http://www.efns.org. Supplementary material presented on http://www.efns.org only is listed as tables S1–S7. The guidelines were prepared following the EFNS criteria (Brainin *et al.*, 2004) and the level of evidence and grade of recommendation are expressed in accordance with this reference. Where there was lack of evidence but consensus was clear we have stated our opinion as good practice points.

1 Diagnosing ALS/MND

Diagnosing ALS is usually considered straight forward if the patient has been ill for some time and has generalized symptoms (Table 1; Li *et al.*, 1986). Diagnosing the disease *early* in the disease when the patient has only limited focal symptoms from one or two regions (bulbar, upper limb, truncal, lower limb) may be difficult and depends on the presence of signs in other affected regions and a number of investigations (Wilbourn, 1998; Meininger, 1999). The mean time from onset of symptoms to confirmation of diagnosis of ALS is 13–18 months (Chio, 1999). Delays may arise from a complex referral pathway, and early symptoms are often intermittent and non-specific and may be denied or go unrecognized by the patient. However, three studies have shown that the longest delay occurs after the patient actually has seen the neurologist (Chio, 1999). There are four cogent reasons for making the diagnosis as early as possible:

For psychological reasons, as the progressive loss of motor symptoms causes anxiety and discomfort,

Table 1 Diagnostic criteria for ALS

The diagnosis of ALS requires the presence of: (positive criteria)
LMN signs (including EMG features in clinically unaffected muscles)
UMN signs
Progression of symptoms and signs
The diagnosis of ALS requires the absence of: (diagnosis by exclusion)
Sensory signs
Sphincter disturbances
Visual disturbances
Autonomic features
Basalganglia dysfunction
Alzheimer-type dementia
ALS 'mimic' syndromes (Table S1)
The diagnosis of ALS is supported by:
Fasciculations in one or more regions
Neurogenic changes in EMG
Normal motor and sensory nerve conduction
Absence of conduction block

impairing the patient's social and professional life; for ethical reasons, so that the patient can better plan the remaining part of her or his life; for economic reasons, as many patients go on a tour of the health care system undergoing series of (expensive) unnecessary tests; for neurological reasons to be able to initiate neuroprotective medication before too many neuronal cells become dysfunctional and lost. Although no hard evidence exists on the kinetics of cell loss in ALS, it is reasonable to assume that the earlier medication is started the greater the neuroprotective effect will be (Bromberg, 1999). Studies in experimental animal models and humans with SOD1 gene mutations indicate that loss of motor neurons is preceded by a period of cellular dysfunction (Aggarwal and Nicholson, 2002). Both in humans and animal models the life prolonging effect of riluzole is greater the earlier medication is initiated. Also, early administration of medication can have a profound positive psychological effect on the patient and carers.

The objective is to present guidelines for making the correct diagnosis and doing this as early as possible. As no single investigation is specific for the diagnosis, carrying out the diagnosis should be based on symptoms, a thorough clinical examination, electrodiagnostic studies, neuroimaging and laboratory studies (Tables 1 and 2; Lima *et al*., 2003). Great care should be taken to rule out diseases that can masquerade as ALS (Table S1; Evangelista *et al*., 1996; Traynor *et al*., 2000). In specialist practice, 5–8% of apparent ALS cases have an alternative diagnosis, which may be treatable in about half the cases (Belsh and Schiffman, 1990; Davenport *et al*., 1996; Traynor *et al*., 2000). Evolution of atypical symptoms or failure of the patient to show progress are the most important 'red flags' suggesting that the diagnosis may be wrong (Traynor *et al*., 2000). The revised El Escorial criteria are research diagnostic criteria for clinical trials (Table 3, adapted from Brooks *et al*., 2000). The criteria are too restrictive for use in routine clinical practice and are not suitable if the objective is to establish the diagnosis as early as possible (Ross *et al*., 1998). In practice, we do not recommend that patients are told they have 'definite, probable or possible' ALS. The clinician must decide, on the balance of probability, whether or not the patient has ALS, even in the absence of unequivocal UMN and LMN signs (Leigh *et al*., 2003).

Good practice points

1 The diagnosis should be pursued as early as possible. Patients with whom ALS is suspected should be referred with high priority to an experienced neurologist.
2 All suspected new cases should undergo prompt detailed clinical and paraclinical examinations (Tables 1 and 2).
3 In some cases, additional investigations may be needed (Table 2).
4 Repetition of the investigations may be needed if the initial series of tests do not result in a diagnosis.
5 Review of the diagnosis is advisable if there is no evidence of progression or if the patient develops atypical features (Table 1).

2 Breaking the news: communicating the diagnosis

Telling the patient and the family that the diagnosis is ALS is a daunting task for the physician. If not performed appropriately, the effect can be devastating, leaving the patient with a sense of abandonment and destroying the patient–physician relationship (Lind *et al*., 1989). Studies of other fatal illnesses (Damian and Tattersall, 1991; Doyle, 1996; Davies and Hopkins, 1997) clearly demonstrated the advantages of utilizing specific techniques (Table 4). Surveys in ALS patients and caregivers have demonstrated that the way the diagnosis is communicated is less than satisfactory in half of the cases (Borasio *et al*., 1998; McCluskey *et al*., 2004). Better performance on all attributes of effective communication as well as greater time spent discussing the diagnosis was correlated with higher patient/caregiver satisfaction (McCluskey *et al*., 2004). A survey in ALS centers has shown that physicians in 44% of center usually spend 30 min or less discussing the diagnosis (Borasio *et al*., 2001a). Callous delivery of the diagnosis may affect the psychological adjustment to bereavement (Ackerman and Oliver, 1997).

Good practice points

1 The diagnosis should be communicated by a consultant with a good knowledge of the patient.

Table 2 Diagnosing ALS/MND: recommended investigations

Clinical chemistry	Test	Evidence class	Recommended mandatory tests	Recommended additional tests in selected cases
Blood	Erythrocyte sedimentation rate	IV	x	
	C-reactive protein (CRP)	IV	x	
	Hematological screen	IV	x	
	ASAT, ALAT, LDH	IV	x	
	TSH, FT4, FT3 hormone assays	IV	x	
	Vitamins B12 and folate	IV	x	
	Serum protein electrophoresis	IV	x	
	Serum immunoelectrophoresis	IV	x	
	Creatine kinase (CK)	IV	x	
	Creatinine	IV	x	
	Electrolytes (Na^+,K^+,Cl^-,Ca^{2+},$PO4^{3-}$)	IV	x	
	Glucose	IV	x	
	Angiotensin converting enzyme (ACE)	IV		x
	Lactate	IV		x
	Hexoaminidase A and B assay	IV		x
	Ganglioside GM-1 antibodies	IV		x
	Anti-Hu, anti-MAG	IV		x
	RA, ANA, anti-DNA	IV		x
	Anti-AChR, anti-MUSK antibodies	IV		x
	Serology (Borrelia, virus including HIV)	IV		x
	DNA analysis (for details see Fig. 1)	IV		x
CSF	Cell count	IV		x
	Cytology	IV		x
	Total protein concentration	IV		x
	Glucose, lactate	IV		x
	Protein electrophoresis including IgG index	IV		x
	Serology (Borrelia, virus)	IV		x
	Ganglioside antibodies	IV		x
Urine	Cadmium	IV		x
	Lead (24 h secretion)	IV		x
	Mercury	IV		x
	Manganese	IV		x
	Urine immunoelectrophoresis	IV		x
Neurophysiology	EMG	III	x	
	Nerve conduction velocity	III	x	
	MEP	IV		x
Radiology	MRI/CAT (head/cervical, thoracic, lumbar)	IV	x	
	Chest X-ray	IV	x	
	Mammography	IV		x
Biopsy	Muscle	III		x
	Nerve	IV		x
	Bone marrow	IV		x
	Lymph node	IV		x

2 The physician should start the consultation by asking what the patient already knows or suspects.

3 Respect the cultural and social background of the patient by asking whether the patient wishes to receive information or prefers that the information be communicated to a family member.

4 The physician should give the diagnosis to the patient and discuss its implications in a stepwise fashion, checking repeatedly if the patient understands what is said, and reacting appropriately to the verbal and non-verbal cues of the patient.

5 The diagnosis should always be given in person and never by mail or telephone, with enough time available (at least 45–60 min) on the part of the physician.

6 Provide printed materials about the disease, about support and advocacy organizations, and about informative websites on the internet. Optionally, a letter or audiotape summarizing what the physician has discussed can be very helpful for the patients and family.

7 Assure the patient that he or her and their family will not be on their own ('abandoned') but will be

Table 3 Revised El Escorial research diagnostic criteria for ALS (summary)

Clinically definite ALS UMN and LMN signs in three regions
Clinically definite ALS – Laboratory supported UMN and/or LMN signs in one region *and* the patient is a carrier of a pathogenic gene mutation
Clinically probable ALS UMN and LMN signs in two regions with some UMN signs rostral to the LMN signs
Clinically probable ALS – laboratory supported UMN signs in one or more regions *and* LMN signs defined by EMG in at least two regions
Clinically possible ALS UMN and LMN signs in one region, or UMN signs in at least two regions, or UMN and LMN signs in two regions with no UMN signs rostral to LMN signs

supported by a professional ALS-care team (where available) and with regular follow-up visits to a neurologist. Make arrangements for a close follow-up visit before the end of the consultation, ideally within 2–4 weeks (or sooner if appropriate).

8 Avoid the following: withholding the diagnosis, providing insufficient information, delivering information callously, or taking away or not providing hope. Remember to switch off mobile phones and pagers, and put up 'Do not disturb' signs.

3 Multidisciplinary care in management of ALS

Specialist multidisciplinary (MD) clinics provide secondary or tertiary services to patients with ALS. These clinics comprise a wide range of health care professionals with expertise in ALS. Ideally, such clinics provide both diagnostic and management services, and facilitate continuity of care by close liaising with the primary care physician and community-based services (Chio *et al*., 2001; Howard and Orrell, 2002; Leigh *et al*., 2003; Traynor *et al*., 2003). The

Table 4 How should a physician tell the patient that they have ALS modified from Miller *et al*. (1999)

Task	Recommendations
Location	Quiet, comfortable, and private
Structure	In person, face-to-face
	Convenient time (at least 45–60 min)
	Enough time to ensure no rushing or interruptions
	Make eye contact and sit close to patient
Participants	Know the patient *before* the meeting including family, emotional and social situation, case history, and all relevant test results. Have all the facts at hand
	Have patient's support network present (relatives). Have a clinical nurse specialist or equivalent present or available
What is said	Find out what the patient already knows about the condition
	Ascertain how much the patient wants to know about ALS and tailor your information accordingly
	Give a warning comment that bad news is coming. The whole truth may need to come by installments
	Use the correct ALS-term, not 'wear and tear of the motor nerves'
	Explain the anatomy of the disease (make a simple drawing)
	If the patient indicates that they want to know the course of the disease, be honest about the probable progression and prognosis but give a broad time frame, and recognize the limitations of any predictions
	There is no cure, symptoms tend to steadily worsen, and prognosis is highly variable. Some patients survives 5 or 10 or more years
	Acknowledge and explore patient's reaction and allow for emotional expression
	Summarize the discussion verbally, in writing, and/or audiotape
	Allow plenty of time for questions
Reassurance	Acknowledge that this is devastating news but discuss reasons for hope such as research, drug trials and the variability of the disease
	Explain that the complications of ALS are treatable
	Reassure that every attempt will be made to maintain the patient's function and that the patient's treatment decisions will be respected
	Reassure that the patient will continue to be cared for and will not be abandoned
	Inform about patient support groups (offer contact details and leaflets)
	Inform about neuroprotective treatment (i.e. riluzole) and ongoing research
	Discuss opportunities to participate in research treatment protocols (if available)
	Acknowledge willingness to get a second opinion if the patient wishes
How it is said	Emotional manner: warmth, caring, empathy, respect
	Be honest, sympathetic but not sentimental
	Give news at person's pace; allow the patient to dictate what he or she is told
Language	Simple and careful word choice, yet direct; no euphemisms or medical jargon

emphasis of care should be on patient autonomy and choice. Patients who attend specialist MD clinics tend to be younger and to have had symptoms for longer than those who do not (Lee *et al.*, 1995; Traynor *et al.*, 2003). Comparisons between clinic-based cohorts and population-based cohorts of patients have confirmed a referral bias (Lee *et al.*, 1995; Traynor *et al.*, 2003). However, an independent survival benefit has been identified in two studies, which is independent of other prognostic factors including age, disease duration, bulbar onset disease and rate of progression (Traynor *et al.*, 2003; Chio *et al.*, 2004a). Importantly, patients attending a multidisciplinary clinic have fewer hospital admissions and shorter durations of stay than those who attend general clinics (Chio *et al.*, 2004a). Increased use of non-invasive ventilation, attention to nutrition and earlier referral to palliative referral services probably contribute to the increased survival of those attending MD clinics (Leigh *et al.*, 2003; Traynor *et al.*, 2003a).

Good practice points

1 Multidisciplinary care should be available for people affected by ALS as attendance at a MD clinic improves care, and may extend survival.
2 The following specialists should be part of or be readily available to the MD team: a consultant in neurology, pulmonologist, gastroenterologist, rehabilitation medicine physician, social counselor, occupational therapist, speech therapist, specialized nurse, physical therapist, dietitian, psychologist, dentist.
3 Schedule clinical visits every 2–3 months and more frequently if needed. This is particularly often the case in the first half year following diagnosis, and in late stages of the disease. Patients with very slowly progressing disease can be seen once or twice a year.
4 It is important that between visits the patient support team maintain regular contact with the patient and relatives (e.g. by phone, letter or email).
5 Ideally, from the outset the patient should be followed by a single named neurologist working in close liason with the patients primary care physician (family general practitioner).
6 Effective channels of communication and co-ordination are essential between the hospital based MD-team, the primary care team, the palliative care team and community services.

4 Neuroprotective treatment

At present, only riluzole, a presumed glutamate-release antagonist, has been shown to slow the course of ALS in two class I studies (Bensimon *et al.*, 1994; Lacomblez *et al.*, 1996; Cochrane review by Miller *et al.*, 2002). Patients with early disease, (i.e. with suspected or possible ALS according to the El Escorial Criteria) were not included. Oral administration of 100 mg riluzole daily prolonged survival by about 3 months after 18 months treatment. There was a clear dose effect. In clinical practice, retrospective phase IV studies from three clinical databases indicate that the overall gain in survival (i.e. over the whole extend of the disease experience), may extend from $\approx$ 6 to 20 months, although these estimates are almost certainly subject to various statistical biases (Brooks *et al.*, 2001; Turner *et al.*, 2002; Traynor *et al.*, 2003b). The drug is safe with few serious side-effects. Guidelines for monitoring have been published (http://www.nice.org.uk/search.aspx?search-mode=simple&ss=ALS). Although patients with progressive spinal muscular atrophy (PMA) or primary lateral sclerosis (PLS) were not included in the riluzole trials, pathological and genetic studies show that some PMA and PLS cases fall within the ALS-syndrome (Fig. 1; Andersen *et al.*, 2003; Brugman *et al.*, 2005). Riluzole may have little effect in late stage ALS and it is not clear if and when treatment should be terminated. A large number of other drugs have been tested in ALS alas with negative results (Table 5).

Good practice points

1 ALS patients should be offered treatment with riluzole 50 mg twice daily (class IA).
2 Patients treated with riluzole should be monitored regularly for safety (class IA).
3 Treatment should be initiated as early as possible after the patient has been informed of the diagnosis taking into account expected therapeutic benefits and potential safety issues (Class IA). Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers.
4 Treatment with riluzole should be considered in PMA and PLS patients who have a first degree relative with ALS.
5 Patients with sporadic PMA, sporadic PLS or HSP should as a rule not be treated with riluzole.
6 Irrespectively of familial disposition, all patients with a symptomatic motor neuron disease and carrying a *SOD1* gene mutation should be offered treatment with riluzole.
7 Currently, there is insufficient evidence to recommend treatment with vitamins, testosterone, anti-oxidants like co-enzyme Q-10 and gingko biloba, intravenous immunoglobuline therapy, cyclosporin, interferones, copaxone, ceftriaxone, minocycline, VEGF, stem cells.

Table 5 Summary of the most important controlled therapeutic studies in ALS

Completed trials
N-acetylcysteine*
Brain-derived neurotrophic factor (BDNF)*
Branched-chain amino acids*
Celecoxib*
Ciliary neurotrophic factor (CNTF)* (two trials)
Creatine* (three trials)
Cyclosporine*
Dextromethorphan*
Gabapentin*
Glial-derived neurotrophic factor (GDNF)*
Indinavir*
Interferon beta-1a*
Insulin-like growth factor (IGF-1)*
Lamotrigine* (two trials)
Lymphoid irradiation*
Nimodipine*
ONO-2506*
Pentoxifylline*
Riluzole
Selegiline*
TCH-346*
Topiramate*
Verapamil*
Vitamin E* (two trials)
Xaliproden*
Ongoing phase II/III trials (summer of 2005)
Arimoclomol
Ceftriaxone
IGF-1 polypeptide
Minocycline
Phase III trials being planned or considered
AEOL 10150
Celastrol
Coenzyme Q10
Copaxone
IGF-1 – viral delivery
Memantine
NAALADase inhibitors
Nimesulide
Scriptaid
Sodium phenylbutyrate
Talampanel
Tamoxifen
Thalidomide
Trehalose

*No therapeutic benefit was observed.

5 Symptomatic treatment

Symptomatic treatment aims to improve the quality of life of patients and care givers. Symptoms should be treated as they become prominent and incapacitating in individual patients.

Sialorrhea

Sialorrhea (drooling or excessive salivation) is a socially disabling symptom. It results from impaired handling of saliva rather than from overproduction. Sialorrhea is treatable. Most evidence, however, comes from studies in other conditions. Amitriptyline is commonly used with reasonable efficacy at low cost (Forshew and Bromberg, 2003). Oral doses of not more than 25–50 mg twice to three times a day are usually sufficient.

Atropine drops can be administered sublingually. A class IV study in seven patients with Parkinson's disease demonstrated statistically significant decline in saliva production (Hyson *et al*., 2002). For ALS patients 0.25–0.75 mg three times a day is recommended empirically (Leigh *et al*., 2003). Glycopyrrolate (in nebulized or iv form) has been shown to be effective in patients with cerebral palsy or developmental disabilities in a class I study (Mier *et al*., 2000), but no studies in ALS are known. Hyoscine (scopolamine) can be given orally or applied as a dermal patch. Two class IV studies (Talmi *et al*., 1989, 1990) showed a reduction of salivary flow with transdermal scopolamine (1.5 mg every 3 day). Patients with severe drooling may need two patches.

Benztropine demonstrated in a class I study in developmentally disabled patients a decrease in drooling up to 70% (Camp-Bruno *et al*., 1989). An alternative to anticholinergic drugs is botulinum toxin: In a class IV study in ALS-patients, Giess *et al*., 2000 showed a reduction of sialorrhea by injections of botulinum toxin type A into the salivary glands. The effect faded in several months, and repeated injections were necessary. Studies with similar results have been carried out in patients with other neurological disorders (Porta *et al*., 2001; Dogu *et al*., 2004). However, serious side-effects have been reported (Tan *et al*., 2001; Winterholler *et al*., 2001). There are no studies using botulinum toxin type B. Another alternative is radiological interventions. Three class IV studies in ALS-patients showed satisfactory results in the treatment of drooling with external radiation of the parotid and submandibular glands (Andersen *et al*., 2001; Harriman *et al*., 2001; Stalpers and Moser, 2002). Low dosage palliative radiation in a single fraction of 7–8 Gy to the parotid glands is a simple, fast, safe and inexpensive procedure to reduce drooling in ALS patients.

Surgical interventions, such as transtympanic neurectomy, parotid duct ligation and relocation and submandibular gland excision, showed effective long-term results in children with drooling (Burton, 1991; Hockstein *et al*., 2004). Case reports suggests less efficacy in ALS patients with reports of increased secretions of thick mucus production and side-effects like recurrent jaw dislocation and inflammation (Janzen *et al*., 1988; Winterholler *et al*., 2001).

Good practice points

1 Treat sialorrhea in ALS with oral or transdermal hyoscine, atropine drops, glycopyrrolate or amitriptyline.
2 Provide a portable mechanical home suction device.
3 Botulinum toxin injections into the parotid glands can be tried but insufficient data are available yet to appraise safety and long-term efficacy, and this intervention is judged as still experimental.
4 Irradiation of the salivary glands may be tried when pharmacological treatment fails.
5 Surgical interventions are not recommended.

Bronchial secretions

Clearing tenacious secretions can be difficult for the patient with respiratory insufficiency causing much distress to the patient. The mucosa of the nasal cavity, larynx, trachea, bronchial airways and lungs contribute a constant flow of serous and particularly mucoid fluids. Stimulation of cholinergic receptors produces thin serous secretions whereas stimulation of β-adrenergic receptors produces thick protein- and mucus-rich secretions. A portable home suction device is useful for clearing the upper airways (and excess saliva in the mouth). However, secretions in the lower airways can be difficult to reach. Medication with mucolytics like guaifenesin or N-acetylcysteine, a β-receptor antagonist (such as metoprolol or propranolol) and/or an anticholinergic bronchodilator like ipratropium and/or theophylline or even furosemide can be of value, but no controlled studies in ALS exist (Newall *et al.*, 1996). Mechanical cough assisting devices (insufflator-exsufflator) via a face mask was very effective in ALS patients in uncontrolled trials (Hanayama *et al.*, 1997; Sancho *et al.*, 2004).

Good practice points

1 Teach the patient and carers the technique of assisting expiratory movements using a manual assisted cough (can also be performed by a physical therapist).
2 Provide a portable home suction device and a room humidifier.
3 Consider using a mucolytic like N-acetylcysteine, 200–400 mg three times daily.
4 If these measures are insufficient, try a nebulizer with saline and a β-receptor antagonist and/or an anticholinergic bronchodilator and/or a mucolytic and/or furosemide in combination.
5 The use of a mechanical insufflator-exsufflator may be helpful, particularly in the setting of an acute respiratory infection.
6 Cricopharyngeal myotomy may be helpful in the rare cases with frequent episodes with cricopharyngeal spasm and severe bronchial secretions.

Pseudobulbar emotional lability

Pseudobulbar signs such as pathological weeping, laughing or yawning can be socially disabling. Emotional lability occurs in at least 50% of ALS patients and can be seen in patients without bulbar motor signs (Gallagher, 1989). Occasionally, the emotional outbursts are more troubling for the relatives and nursing staff than the patient, and treatment may not be necessary. A randomized controlled trial of a combination of dextrometorphan and quinidine showed this to be effective in improving emotional lability and quality of life (Brooks *et al.*, 2004). Side-effects were experienced by 89% of patients and 24% discontinued treatment during the trial's 4-week duration. Fluvoxamine (Iannaccone and Ferini-Strambi, 1996), amitriptyline, citalopram and even dopamine and lithium have been tested with good effect in other neurological diseases (Schiffer *et al.*, 1985; Andersen *et al.*, 1993). There appears to be no advantage for a particular medication so the emphasis should be on tolerability, safety and cost.

Good practice points

1 Inform the patient and relatives that the emotional lability is not a sign of a mood disorder but is due to an organic lesion in the brain (Poeck, 1996).
2 Only troublesome emotional lability should be treated. If treatment is deemed necessary, an antidepressant such as amitriptyline, fluvoxamine, citalopram is usually sufficient.
3 A combination of dextrometorphan and quinidine has been shown to be effective in a class IA study but further experience on the long-term side-effects and tolerability are needed.

Cramps

Cramps may be an early and troublesome symptom in ALS, in particular before falling asleep. Class I studies in patients with non-ALS leg cramps with quinine sulfate and vitamin E (Connolly *et al.*, 1992; Diener *et al.*, 2002) showed a positive effect only for quinine. Empirically, massage, physical exercise (in the evening), hydrotherapy, Mg^{2+}, carbamazepine, diazepam, phenytoin, verapamil, gabapentin can alleviate muscle cramps.

Good practice points

1 Treat cramps in ALS with physiotherapy, physical exercise and/or hydrotherapy.

2 If necessary, treat cramps in ALS with quinine sulfate.
3 Mg^{2+}, carbamazepine, phenytoin, verapamil, gabapentin are alternatives.

Spasticity

Spasticity can be a troublesome symptom in patients with ALS. Physical therapy is vital and helped reducing spasticity in a class IIB study (Drory *et al*., 2001). Modalities such as hydrotherapy, heat, cold, ultrasound, electrical stimulation, and in rare cases surgery can be used, although no controlled studies in ALS exist. In a class III study of 20 patients with spinal cord injury, the use of hydrotherapy in heated pools three times per week produced a significant decrease in spasm severity and reduction of oral baclofen medication (Kesiktas *et al*., 2004). Cryotherapy of the facial muscles reduced spasticity to facilitate dental care in 24 patients with cerebral palsy (dos Santos and de Oliveira, 2004). Oral baclofen (up to 80 mg daily) revealed no significant effect in spasticity in ALS in one small study (Norris *et al*., 1979). Intrathecal baclofen in two ALS-patients with intractable spasticity was more effective than oral medication and greatly improved the patient's quality of life (Marquardt and Seifert, 2002). Other drugs have not been tested formally in ALS, but in clinical practice gabapentin (900–2400 mg daily), tizanidine (6–24 mg daily), memantine (10–60 mg daily), dantrolene (25–100 mg daily) and diazepam (10–30 mg daily) have been used with effect. Botulinum toxin A has successfully been used to treat trismus and stridor in case reports (Winterholler *et al*., 2002).

Good practice points

1 Physical therapy should be available regularly when there is significant spasticity.
2 Hydrotherapy with exercises in heated pools with 32–34°C warm water, and cryotherapy should be considered.
3 Antispastic drugs such as baclofen and tizanidine may be tried.

Depression, anxiety and insomnia

Depression occurs frequently at all stages of ALS as well as insomnia (Dengler, 1999). Anxiety can become marked when respiratory insufficiency occurs. The four mostly used antidepressants in ALS are amitriptyline, sertraline, fluoxetine and paroxetine. Amitriptyline has the best therapeutic effect and the lowest costs. For insomnia in ALS, amitriptyline and zolpidem are the most commonly used medications (Forshew and Bromberg, 2003). There are no systematic studies on anxiolytics in ALS, but oral diazepam or sub-lingual lorazepam are useful.

Good practice points

1 Treat depression in ALS with an appropriate antidepressant, e.g. amitriptyline or an SSRI.
2 Treat insomnia with amitriptyline or appropriate hypnotics (e.g. zolpidem, diphenhydramine).
3 Treat anxiety with bupropion or benzodiazepines such as diazepam tablets or suppositories, temesta tablets 0.5 mg two to three times daily, or lorazepam sublingually.

Pain

Pain occurs frequently in ALS. Some familial ALS syndromes include pain of neuralgic type. Treatment is unspecific and should follow accepted principles. Opioids can be used, following the 1990-WHO analgesic ladder guidelines, when non-narcotics fail (Miller, 2001): Begin with simple analgesics such as paracetamol, followed by weak opioids such as tramadol, followed by strong opioids such as morphine or ketobemidon. Liberal use of opioids may be appropriate when non-narcotics fail and have the secondary advantages of alleviating dyspnea and anxiety. However, constipation may become a problem.

Good practice point

Treat pain in ALS following accepted guidelines.

Venous thrombosis

Patients with leg paralysis have an increased risk of venous thrombosis.

Good practice points

Physiotherapy, limb elevation, compression stockings can be used. Prophylactic treatment with anti-coagulants is not recommended.

6 Genetic testing and counseling

In different populations, the frequency of FALS is reportedly 5–10% of all ALS cases (Table 6) but may be underestimated for a number of reasons (Table S2). Presently four genes have been found to cause ALS (Figs 1 and 2), *SOD1*, *VAPB*, *SETX* and *ALSIN*. At present mutations in the latter three genes appears to be very rare and analysis is only performed in a scientific setting.

Since 1993 some 119 mutations have been found in the *SOD1* gene with five different modes of inheritance (Fig. 2; http://www.ALSOD.org; Andersen *et al*., 2003). The most frequent mutation is the *D90A*, which in most European countries is inherited as a recessive trait with a characteristic slowly progressing phenotype (Andersen *et al*., 1996). Twelve to 23% of diagnosed FALS and 2–7% of apparently SALS

Table 6 Frequency of FALS in some epidemiological studies

Study area	% FALS	*n*	Year	Reference
Germany	13.5	251	1959	Haberlandt (1959)
central Finland	11.6	36	1983	Murros and Fogelholm (1983).
USA	9.5	1200	1995	Haverkamp *et al.* (1995)
Belgium	8.6	140	2000	Thijs *et al.* (2000)
Nova Scotia, Canada	5.8	52	1974	Murray *et al.* (1974)
Wärmland, Sweden	5.6	89	1984	Gunnarsson and Palm (1984)
England	5.0	580	1988	Li *et al.* (1988)
USA	4.9	668	1978	Rosen (1978)
northern Sweden	4.7	128	1983	Forsgren *et al.* (1983)
Sardinia, Italy	4.4	182	1983	Giagheddu *et al.* (1983)
Jutland, Denmark	2.7	186	1989	Højer-Pedersen *et al.* (1989)
Hong Kong	1.2	84	1996	Fong *et al.* (1996)
Finland	0.8	255	1977	Jokelainen (1977)

patients carry a *SOD1* mutation (Table 7). It must be emphasized that diminished disease penetrance is not infrequent and that *SOD1* mutations can be found in cases of apparently SALS (Tables S3 and S4; Jones *et al.*, 1995). A DNA-SOD1 diagnostic test speeds up the diagnostic process and can be of help in patients with atypical features (Andersen *et al.*, 2003) as well as providing some prognostic information (Tables S5 and S6; Andersen *et al.*, 1996). Pre-symptomatic (predictive) genetic testing should only be performed in first degree adult blood-relatives of patients with a known *SOD1* gene mutation. Testing should only be performed on a strictly volunteer basis as outlined (Table S7; Gasser *et al.*, 2001). Special

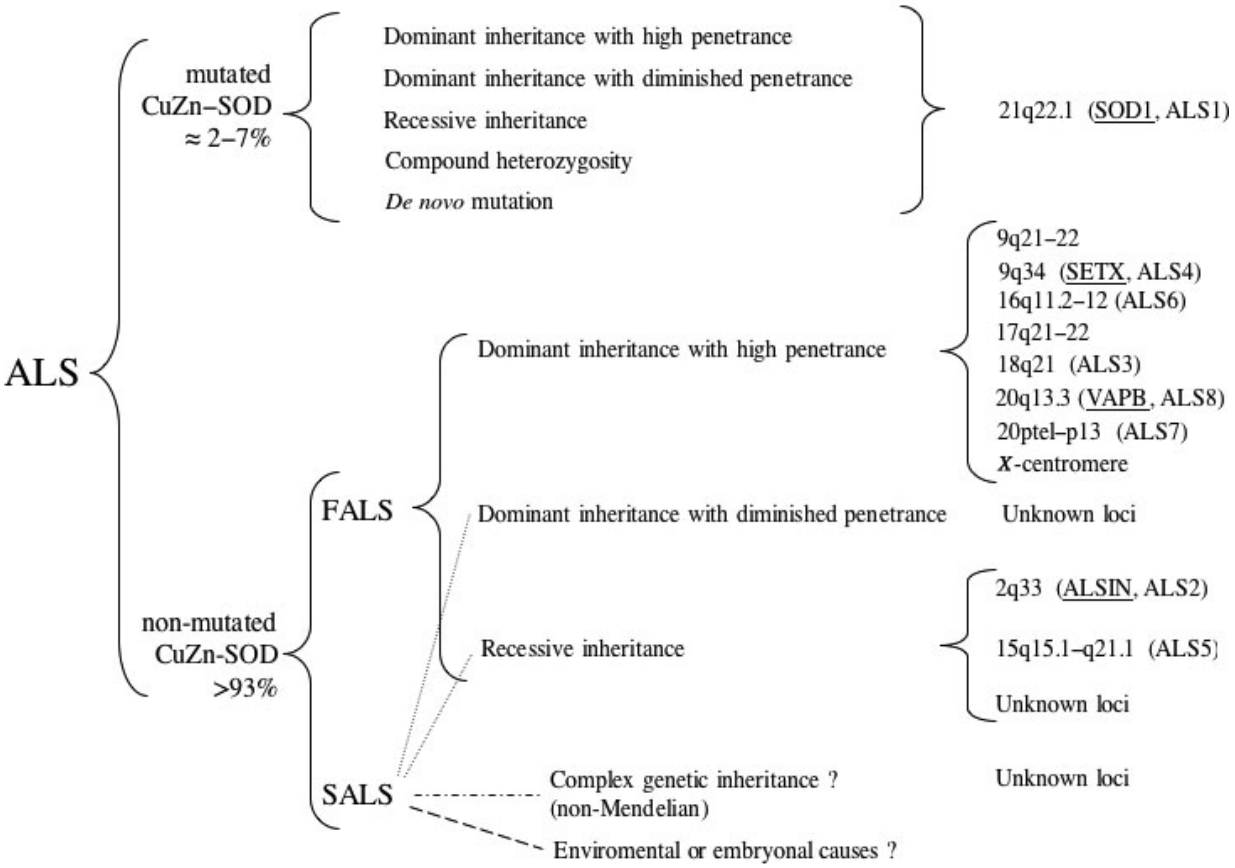

Figure 2 The different patterns of inheritance and genetic loci found in ALS. It is important to remember that reduced disease penetrance has been recognized in many families with ALS. Some cases diagnosed as SALS are in fact FALS with very low disease penetrance, recessive inheritance or oligogenic inheritance in a complicated pattern not always understood. CuZn–SOD, SOD1, copper-zinc superoxide dismutase.

Table 7 Frequency of CuZn-SOD (SOD1) mutations in ALS

In SALS
7.3% (3/41) in Italy (Corrado L. et al., personal communication June 2005)
7% (4/56) in Scotland (Jones *et al*., 1995)
6% (3/48) in Italy (Gellera, 2001)
4% (14/355) in Scandinavia (Andersen *et al*., 1997)
3% (5/175) in the UK (Shaw *et al*., 1998)
3% (5/155) in England (Jackson *et al*., 1997)
1.2% (1/87) in Spain (Garcia-Redondo *et al*., 2002)
0% (0/225) in Italy (Battistini *et al*., 2005)
In FALS
23.5% (12/51) in Scandinavia (Andersen *et al*., 1997)
23.5% (68/290) in the USA (Cudkowicz *et al*., 1997)
21% (8/38) in the UK (Shaw *et al*., 1998)
19.7% (14/71) in the UK (Orrell *et al*., 1997)
18% (2/11) in Spain (Garcia-Redondo *et al*., 2002)
18% (7/39) in Italy (Battistini *et al*., 2005)
14.3% (10/70) in France (Boukaftane *et al*., 1998)
12% (9/75) in Germany (Niemann *et al*., 2004)

Without classification to hereditary disposition: 7.2% (148/2045) in North America (Andersen *et al*., 2003).

consideration should be taken before pre-symptomatic testing is performed in FALS families where the mutation is associated with reduced disease penetrance (Table S3) or with a variable prognosis (Table S5).

Good practice points

1 Clinical DNA analysis for *SOD1* gene mutation should only be performed in cases with a known familial history of ALS or in SALS cases with the characteristic phenotype of the *D90A* mutation.
2 Clinical DNA analysis for *SOD1* gene mutations should *not* be performed in cases with SALS with a typical classical ALS-phenotype.
3 Before blood is drawn for DNA analysis, the patient should receive genetic counseling. Give the patient time for consideration. DNA analysis should not be performed without the patients consent.
4 Pre-symptomatic genetic testing should *only* be performed in first degree adult blood-relatives of patients with a known *SOD1* gene mutation. Testing should only be performed on a strictly volunteer basis as outlined (Table S7).
5 Results of DNA analysis performed on patients and their relatives as part of a research project should not be used in clinical practice or disclosed to the unaffected relative. Also, the results should be kept in a separate file, not in the patient's medical chart.

7 Non-invasive and invasive ventilation in ALS patients

Respiratory insufficiency in ALS patients is caused mainly by respiratory muscle or bulbar weakness and can be aggravated by aspiration and bronchopneumonia (Howard and Orrell, 2002). Some patients present with thoracic paresis and respiratory insufficiency (Table 8). Vital capacity (VC) is the most widely available test of respiratory muscle function and should be measured regularly in parallel with assessments of symptoms suggestive of respiratory insufficiency (Leigh *et al*., 2003). Sniff nasal pressure (SNP) may be a more accurate predictor of respiratory failure than VC, but neither VC nor SNP are sensitive predictors of respiratory failure in patients with severe bulbar involvement (Lyall *et al*., 2001). Nocturnal oximetry can detect nocturnal hypoventilation and can be done at home. Blood exchange abnormalities ($\uparrow PCO_2$) are generally a late finding. Non-invasive positive-pressure ventilation (NIV) and invasive mechanical ventilation via tracheostomy (TV) are used to alleviate respiratory symptoms, improve quality of life and prolong survival. There is no clear evidence regarding timing and criteria of use of NIV and TV in ALS patients (Table 9). The use of mechanical ventilation varies between countries with cross-cultural and ethical differences (Miller *et al*., 1999; Bourke and Gibson, 2004). The patient's advance directives and a clear plan for management of respiratory failure should be established before respiratory failure occurs (Miller *et al*., 1999; Leigh *et al*., 2003; Bourke and Gibson, 2004). The choice of ventilation will depend on hypoventilation symptoms and upper airway obstruction symptoms, bronchial secretions and factors such as availability, cost, patient preference and care.

NIV has become the preferred initial therapy to alleviate respiratory symptoms in ALS patients and should be considered before TV (Miller *et al*., 1999; Annane *et al*., 2000; Leigh *et al*., 2003; Bourke and

Table 8 Symptoms and signs of respiratory insufficiency in ALS [modified from Leigh *et al*. (2003)]

Symptoms	Signs
Dyspnoea on exertion or talking	Tachypnea
Ortopnoea	Use of auxillary respiratory muscles
Frequent nocturnal awakenings	Paradoxical movement of abdomen
Excessive daytime sleepiness	Decreased chest movement
Daytime fatigue	Weak cough
Difficulty clearing secretions	Sweating
Morning headache	Tachycardia
Nocturia	Weight loss
Depression	Confusion, hallucinations, dizziness
Poor appetite	Papilloedema (rare)
Poor concentration and/or memory	Syncope
	Mouth dryness

Table 9 Proposed criteria for NIV [modified from Leigh *et al.* (2003)]

1 Symptoms related to respiratory muscle weakness. At least one of the following:
(a) Dyspnoea
(b) Orthopnoa
(c) Disturbed sleep not because of pain
(d) Morning headache
(e) Poor concentration
(f) Loss of appetite
(g) Excessive daytime sleepiness (ESS > 9)
2 Signs of respiratory muscle weakness (FVC < 80% or SNP < 40 cm H_2O)
3 Evidence of either:
(a) Significant nocturnal desaturation on overnight oximetry, *or*
(b) Morning blood-gas pCO2 >6.5 Kpa.

ESS, Epworth Sleepiness Score.

Gibson, 2004). It is usually initially used for intermittent nocturnal support to alleviate symptoms of nocturnal hypoventilation (Table 8). Observational studies suggest that NIV improves survival and quality of life (Bourke *et al.*, 2003). Secretion management is a major factor in the success of NIV (Leigh *et al.*, 2003), (see section Bronchial secretions). As respiratory muscle strength declines, daytime NIV usually becomes necessary and patients may become dependent on non-stop ventilation. Patients who cannot use NIV should be informed about the terminal phase, TV, hospice referral and palliative care. Patients with flaccid paresis of the facial muscles may have difficulty using NIV, but the method should be offered to patients with predominating UMN bulbar paresis and little atrophy.

TV may be proposed when NIV treatment is not effective because of progression of the disease or when the patient cannot cooperate with NIV because of loss of bulbar tone and difficulty clearing secretions (Fig. 3; Miller *et al.*, 1999). TV can prolong survival for many years, can be acceptable for some patients and caregivers and in these cases can improve patients' quality of life, although some patients become unable to communicate in a state of locked-in (Leigh *et al.*, 2003). However, home TV is costly and has a significant emotional and social impact on patients and caregivers (Cazzolli and Oppenheimer, 1996; Miller *et al.*, 1999). The advantages and drawbacks of TV are summarized in Table 10. A difficult issue is when to terminate ventilatory support. Parenteral diamorphine, a benzodiazepine and an antiemetic are used when the patient decides that ventilatory support should be withdrawn (Miller *et al.*, 1999). For symptomatic treatment of dyspnea with opioids and/or oxygen, the class of evidence is IA in cancer and chronic obstructive pulmonary disease (Jennings *et al.*, 2002; Bruera *et al.*, 2003), but no controlled studies in ALS exist.

Good practice points

1 Symptoms or signs of respiratory insufficiency (including symptoms of nocturnal hypoventilation) should be checked at each visit.

2 VC is the most available and practical test for the monitoring of respiratory function on a regular basis. If possible, VC should be measured both standing/sitting and lying.

3 SNP may be used for monitoring of inspiratory muscle strength, particularly in some bulbar patients who cannot perform VC accurately.

4 Nocturnal oximetry, available at home, is recommended in patients with symptoms of nocturnal hypoventilation.

5 Symptoms or signs of respiratory insufficiency should initiate discussions with the patient and the caregivers about all treatment options such as NIV, TV and the terminal phase. Early discussions are needed to allow advance planning and directives. The patient should be informed about the

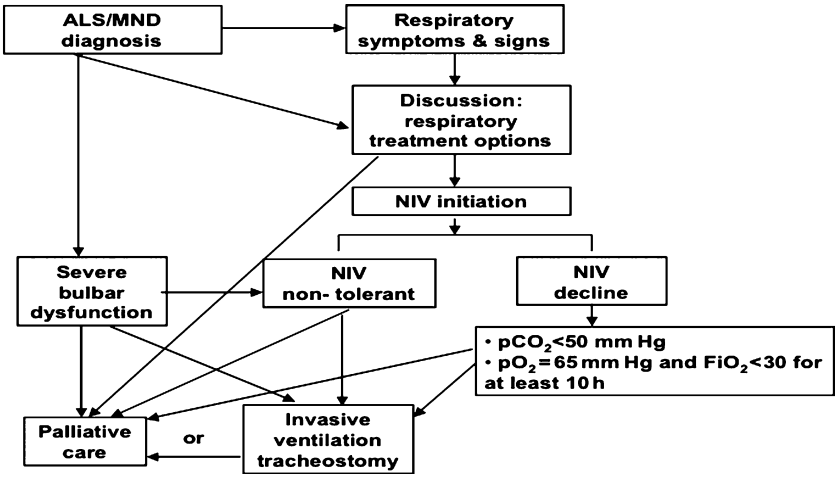

Figure 3 Flowchart for the management of respiratory dysfunction in ALS.

Table 10 The advantages and drawbacks of invasive ventilation tracheostomy

1 Advantages
(a) preventing aspiration
(b) more secure ventilator – patients interface
(c) ability to provide higher ventilator pressures
2 Drawbacks
(a) more secretions generating
(b) impairing swallowing risk
(c) increasing aspiration
(d) increasing risk of infections
(e) tracheoesophageal fistula
(f) tracheal stenosis or tracheomalacia
(g) costs
(h) 24 h nursing care

temporary nature of NIV [which is primarily directed towards improving quality of life rather than prolonging it (as opposed to TV)]. Care should adapt to the changing needs of patients and carers over the course of the disease.

6 NIV should be considered before TV in patients with symptoms of respiratory insufficiency.

7 TV can prolong survival for many months and can improve patient's quality of life, but it has major impact upon carers, and be undertaken only after full discussion of the pro's and con's with the patient and carers.

8 Unplanned (emergency) TV should be avoided at all costs through early discussion of end of life issues, palliative care, and advance directives.

9 Oxygen therapy alone should be avoided as it may exacerbate CO_2 retention and mouth dryness.

10 Medical treatment of intermittent dyspnea:

- short dyspneic bouts: relieve anxiety and give lorazepam 0.5-2.5 mg sublingually
- longer phases of dyspnea (>30 min): give morphine.

11 Medical treatment of chronic dyspnea: start with morphine 2.5 mg orally four to six times daily. For severe dyspnea give morphine sc or iv infusion. Start with 0.5 mg/h and titrate.

8 Enteral nutrition in ALS patients

Initial management of dysphagia in patients with ALS is based on dietary counseling, modification of food and fluid consistency (blending food, adding thickeners to liquids), prescription of high protein and caloric supplements and education of the patient and carers in feeding and swallowing techniques such as supraglottic swallowing and postural changes (Miller *et al*., 1999; Desport *et al*., 2000; Heffernan *et al*., 2004). Flexing the neck forward on swallowing to protect the airway ('chin tuck maneuver') may be helpful. Some patients having difficulty swallowing tap water can drink carbonated fluids or ice-cold fluids. Empirically, this is particular the case for patients with predominantly spastic dysphagia. Sufficient oral fluid intake is important also to improve articulation, to maintain good oral hygiene and reduce the risk of constipation. As dysphagia progresses, these measures become insufficient and tube feeding is needed. Three procedures obviate the need for major surgery and general anesthesia: percutaneous endoscopic gastrostomy (PEG), percutaneous radiologic gastrostomy (PRG or RIG, radiologically inserted gastrostomy) and nasogastric tube (NGT) feeding.

The PEG is the standard procedure for enteral nutrition in ALS and is wildly available (Desport *et al*., 2000; Heffernan *et al*., 2004). PEG improves nutrition, but there is no convincing evidence that PEG prevents aspiration or improves quality of life or survival (Miller *et al*., 1999; Heffernan *et al*., 2004). The procedure requires mild sedation and is therefore more hazardous in patients with respiratory impairment and/or at an advanced stage of the disease (Miller *et al*., 1999; Desport *et al*., 2000; Heffernan *et al*., 2004). Non-invasive ventilation during the PEG procedure may be feasible in ALS patients with respiratory impairment (Heffernan *et al*., 2004). The timing of PEG is mainly based on symptoms, nutritional status and respiratory function (Miller *et al*., 1999; Heffernan *et al*., 2004). To minimize risks, evidence suggests that PEG should be performed before VC falls below 50% of predicted (Mathus-Vliegen *et al*., 1994).

PRG is a new alternative to PEG in ALS patients (Chio *et al*., 2004b; Heffernan *et al*., 2004; Shaw *et al*., 2004). A major advantage of PRG is that it does not require sedation and therefore is suitable in patients with respiratory impairment or in poor general condition. The success rate of PRG procedure has also been shown to be higher than PEG (Thornton *et al*., 2002; Chio *et al*., 2004b). However, this procedure is not yet widely available and is less well documented than PEG.

The NGT is a minor and non-invasive procedure that can be given to all patients but presents numerous disadvantages that limit its use (Scott and Austin, 1994; Heffernan *et al*., 2004). NGT increases oropharyngeal secretions and is associated with nasopharyngeal discomfort, pain or even ulceration.

Good practice points

1 Bulbar dysfunction and nutritional status, including at least weight, should be checked at each visit.

2 The patient and spouse should be referred to a dietician as soon as dysphagia appears. A speech and language therapist (SLT) can give valuable advice on swallowing techniques.

3 The timing of PEG/PRG is based on an individual approach taking into account bulbar symptoms, malnutrition (weight loss $>10\%$), respiratory function and the patient's general condition. Thus, early operation is highly recommended.
4 When PEG is indicated, patient and carers should be informed: (i) of the benefits and risks of the procedure; (ii) that it is possible to continue to take food orally as long as it is possible; (iii) that deferring PEG to a late disease stage may increase the risk of the procedure.
5 Percutaneous radiologic gastrostomy (PRG; RIG) is a suitable alternative to PEG. This procedure can be used as the procedure of choice or when PEG is deemed hazardous.
6 Tubes with relatively large diameter (e.g. 18–22 Charriere) is recommended for both PEG and PRG in order to prevent tube obstruction.
7 Prophylactic medication with antibiotics on the day of the operation may reduce the risk of infections.
8 NGT may be used for short-term feeding and when PEG or PRG is not suitable.

9 Communication in ALS patients

Most commonly communication difficulties in ALS result from progressive dysarthria, with language functions remaining largely intact. However, changes of language function may occur, especially in patients with cognitive impairment of frontal type. This is shown by reduced verbal output (in rare cases leading to mutism), reduced spelling ability, word finding difficulty and auditory comprehension of more complex input (Bak and Hodges, 2004). In others, the deficits are subtle and only exposed on formal testing (Cobble, 1998). Language impairment can have a deleterious effect on the quality of life of the patients and carers, and can make the clinical management of the patient difficult (Cobble, 1998; Murphy, 2004).

Communication should be routinely assessed by a speech therapist. The goal of management of communication difficulties in ALS patients is to optimize the effectiveness of communication for as long as possible and to concentrate not only on the disabled person, but on personal partner-to-partner communication as well. When dysarthria progresses the use of an augmentive and alternative communication (AAC) system is needed. An ACC system substantially improves the quality of life. Prosthetic treatments (palatal lift and/or palatal augmentation prosthesis) can be useful in reduction of hypernasality and improvement of articulation. For ventilated patients eye-pointing or eye-gaze augmentive high-tech communication devices are useful. Brain-computer-interfaces, EEG & EP (SCP) methods, thought translation devices can be used as the new communication channels.

Good practice points

1 Regular assessment (i.e. every 3–6 months) of communication by a trained speech therapist is recommended.
2 The use of appropriate communication support systems (ranging from pointing boards with figures or words, to computerized speech synthesizers) should be provided as required.

10 Palliative and end-of-life care

A palliative care approach should be incorporated into the care plan for patients and carers from the time of diagnosis (Borasio *et al.*, 2001b, class III recommendation). Early referral to a specialist palliative care team is often appropriate. Palliative care based in the community or through hospice contacts (e.g. home care teams) can proceed in partnership with clinic-based neurological multidisciplinary care. The aim of palliative care is to maximize quality of life of patients and families by relieving symptoms, providing emotional, psychological and spiritual support as needed, removing obstacles to a peaceful death, and supporting the family in bereavement (Oliver *et al.*, 2000). Various other aspects of terminal care have been covered in sections 5, 7, 8 and 9.

Good practice points

1 Whenever possible, offer input from a palliative care team early in the course of the disease.
2 Initiate discussions on end-of-life decisions whenever the patient asks – or 'opens the door' – for end-of-life information and/or interventions.
3 Discuss the options for respiratory support and end-of-life issues if the patient has dyspnea, other symptoms of hypoventilation (Table 8), or a forced VC $<50\%$.
4 Inform the patient of the legal situation regarding advance directives and naming of a health care proxy. Offer assistance in formulating an advance directive.
5 Re-discuss the patient's preferences for life-sustaining treatments every 6 months.
6 Initiate early referral to hospice or home care teams well in advance of the terminal phase of ALS to facilitate the work of the hospice team.
7 Be aware of the importance of spiritual issues for the quality of life and treatment choices. Establish a liaison with local pastoral care workers in order to be able to address the needs of the patient and relatives.

8 For symptomatic treatment of dyspnea and/or pain of intractable cause use opioids alone or in combination with benzodiazepines if anxiety is present. Titrating the dosages against the clinical symptoms will almost never result in a life-threatening respiratory depression (Sykes and Thorns, 2003, class IA recommendation).
9 For treating terminal restlessness and confusion because of hypercapnia neuroleptics may be used, (e.g. chlorpromazine 12.5 mg every 4–12 h po, iv or pr).
10 Use oxygen only if symptomatic hypoxia is present.

Future developments

Being a syndrome with low incidence and short survival, most recommendations are good practice points based on consensus of experts in the ALS field. More preferably randomized and double-blinded clinical trials are urgently needed to improve the management of ALS.

Research recommendations

1 Further studies of more specific diagnostic tools are needed, in particular in relation to cervical spondylotic myelopathy, inclusion body myositis and motor neuropathies.
2 There is no data on the effects of MD clinics on quality of life or care burden – the generation of such data would be beneficial.
3 Further studies are required to confirm the benefits of MD clinics, and to identify the factors that affect outcome.
4 Further studies are required to optimize the symptomatic treatment of ALS patients, in particular therapies for treating muscle cramps, drooling and bronchial secretions.
5 Better criteria for defining the use of PEG and PRG, and NIV and TV are urgently needed.
6 Further studies to evaluate the effects of PEG/PRG, cough-assisting devices and ventilation support on quality of life and survival are advocated.
7 Further studies are required to evaluate the language dysfunction and it's treatment in ALS.
8 Studies of the medico-economical impact of more expensive procedures (NIV, TV, cough-assisting devices, advanced communication equipment) are needed.

These guidelines will be updated when necessary and in any case in not more than 3 years.

Conflicts of interest

The present guidelines were prepared without external financial support. None of the authors report conflicting interests.

Supplementary Material

The following material is available online at http://www.blackwell-synergy.com:

Table S1 Diseases that can masquerade as ALS/MND

Table S2 Factors that may lead to underrepresentation of FALS cases

Table S3 Disease penetrance in ALS associated with a *SOD1* gene mutation

Table S4 *SOD1* gene mutations reported in patients with apparently sporadic ALS (SALS)

Table S5 Disease survival time in ALS associated with *SOD1* gene mutations (without artificial ventilation; Het, heterozygous; hom, homozygous)

Table S6 *SOD1* gene mutations associated with atypical features of ALS (like neuralgic pain syndrome, heat sensations, bladder disturbance)

Table S7 Guidelines for pre-symptomatic genetic testing in ALS

References

Previous guidelines or recommendations are indicated by '*'.

Abrahams S, Goldstein LH, Kew JJ *et al.* (1996). Frontal lobe dysfunction in amyotrophic lateral sclerosis. A PET study. *Brain* **119:**2105–2120.

Ackerman GM, Oliver D (1997). Psychosocial support in an outpatient clinic. *Palliat Med* **11:**167–168.

Aggarwal A, Nicholson G (2002). Detection of preclinical motor neurone loss in SOD1 mutation carriers using motor unit number estimation. *J Neurol Neurosurg Psychiatry* **73:**199–201.

Andersen G, Vestergaard K, Riis JO (1993). Citalopram for post-stroke pathological crying. *Lancet* **342:**837–839.

Andersen PM, Forsgren L, Binzer M *et al.* (1996). Autosomal recessive adult-onset ALS associated with homozygosity for Asp90Ala CuZn-superoxide dismutase mutation. A clinical and genealogical study of 36 patients. *Brain* **119:**1153–1172.

Andersen PM, Nilsson P, Keränen M-L *et al.* (1997). Phenotypic heterogeneity in MND-patients with CuZn-superoxide dismutase mutations in Scandinavia. *Brain* **10:**1723–1737.

Andersen PM, Grönberg H, Franzen L, Funegård U (2001). External radiation of the parotid glands significantly reduces drooling in patients with motor neurone disease with bulbar paresis. *J Neurol Sci* **191:**111–114.

Andersen PM, Sims KB, Xin WW *et al.* (2003). Sixteen novel mutations in the gene encoding CuZn-superoxide dismutase in ALS. *Amyotrop Lateral Scler Other Motor Neuron Disord* **2:**62–73.

Annane D, Chevrolet JC, Chevret S, Raphael JC (2000). Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. *Cochrane Database Syst Rev* (2):CD001941.

Bak TH, Hodges JR (2004). The effects of motor neurone disease on language: further evidence. *Brain Lang* **89:**354–361.

Battistini S, Giannini F, Greco G *et al.* (2005). SOD1 mutations in amyotrophic lateral sclerosis: results from a multicenter Italian study. *J Neurol* **252:**782–788.

Belsh JM, Schiffman PL (1990). Misdiagnosis in patients with amyotrophic lateral sclerosis. *Arch Intern Med* **150:**2301–2305.

Bensimon G, Lacomblez L, Meininger V *et al.* (1994). A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. *N Engl J Med* **330:**585–591.

Bobowick AR, Brody JA (1973). Epidemiology of motor-neuron diseases. *N Engl J Med* **288:**1047–1055.

Borasio GD, Sloan R, Pongratz DE (1998). Breaking the news in amyotrophic lateral sclerosis. *J Neurol Sci* **160**(Suppl. 1)**:**S127–S133.

Borasio GD, Shaw PJ, Hardiman O, Ludolph AC, Sales Luis ML, Silani V, for the European ALS Study Group (2001a). Standards of palliative care for patients with amyotrophic lateral sclerosis: results of a European survey. *Amyotroph Lateral Scler Other Motor Neuron Disord* **2:**159–164.

Borasio GD, Voltz R, Miller RG (2001b). Palliative care in amyotrophic lateral sclerosis. *Neurol Clin* **19:**829–847.

Boukaftane Y, Khoris J, Moulard B *et al.* (1998). Identification of six novel SOD1 gene mutations in familial amyotrophic lateral sclerosis. *Can J Neurol Sci* **25:**192–196.

Bourke SC, Gibson GJ (2004). Non-invasive ventilation in ALS: current practice and future role. *Amyotroph Lateral Scler Other Motor Neuron Disord* **5:**67–71.

Bourke SC, Bullock RE, Williams TL, Shaw PJ, Gibson GJ (2003). Noninvasive ventilation in ALS: indications and effect on the quality of life. *Neurology* **61:**171–177.

Brainin M, Barnes M, Baron J-C *et al.* (2004). Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. *Eur J Neurol* **11:**577–581.

Bromberg M (1999). Accelerating the diagnosis of amyotrophic lateral sclerosis. *Neurologist* **5:**63–74.

Brooks BR, Belden DS, Roelke K *et al.* (2001). Survival in Non-Riluzole treated ALS patients is identical before and since 1996: a clinic-based epidemiological study. *Amyotrophic lateral sclerosis and other motor neuron disorders* **2**(Suppl. 2)**:**60–61 (abstract P15).

Brooks BR, Miller RG, Swash M *et al.* (2000). El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* **1:**293–299.

Brooks BR, Thisted RA, Appel SH *et al.* (2004). Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: a randomized trial. The AVP-923 ALS Study Group. *Neurology* **63:**1364–1370.

Bruera E, Sweeney C, Willey J *et al.* (2003). A randomized controlled trial of supplemental oxygen versus air in cancer patients with dyspnea. *Palliat Med* **17:**659–663.

Brugman F, Wokke JH, Vianney de Jong JM, Franssen H, Faber CG, Van den Berg LH (2005). Primary lateral sclerosis as a phenotypic manifestation of familial ALS. *Neurology* **64:**1778–1779.

Burton MJ (1991). The surgical management of drooling. *Dev Med Child Neurol* **33:**1110–1116.

Camp-Bruno JA, Winsberg BF, Green-Parsons AR, Abrams JP (1989). Efficacy of benztropine therapy for drooling. *Dev Med Child Neurol* **31:**309–319.

Cazzolli PA, Oppenheimer EA (1996). Home mechanical ventilation for amyotrophic lateral sclerosis: nasal compared to tracheostomy-intermittent positive pressure ventilation. *J Neurol Sci* **139**(Suppl.)**:**123–128.

Chio A (1999). Survey: an international study on the diagnostic process and its implications in amyotrophic lateral sclerosis. *J Neurol* **246**(Suppl. 3)**:**III1–5.

Chio A, Silani V, Italian ALS Stud Group (2001). ALS care in Italy: a nationwide study in neurological centres. *J Neurol Sci* **191:**145–150.

Chio A, Moral G, Balzarino C, Mutani R (2004a). Interdisciplinary ALS Centres: effect of survival and use of health services in a population-based survey. *Neurology* **62**(5)**:**S23.003 (Abstract).

Chio A, Galletti R, Finocchiaro C *et al.* (2004b). Percutaneous radiological gastrostomy: a safe and effective method of nutritional tube placement in advanced ALS. *J Neurol Neurosurg Psychiatry* **75:**645–647.

Cobble M (1998). Language impairment in motor neurone disease. *J Neurol Sci* **160**(Suppl. 1)**:**S47–52.

Connolly PS, Shirley EA, Wasson JH, Nierenberg DW. (1992). Treatment of nocturnal leg cramps. A crossover trial of quinine vs vitamin E. *Arch Intern Med* **152:**1877–1880.

Cudkowicz ME, McKenna-Yasek D, Sapp PE *et al.* (1997). Epidemiology of mutations in superoxide dismutase in amyotrophic lateral sclerosis. *Ann Neurol* **41:**210–221.

Damian D, Tattersall MHN (1991). Letters to patients: improving communication in cancer care. *Lancet* **338:**923–925.

Davenport RJ, Swingler RJ, Chancellor AM, Warlow CP (1996). Avoiding false positive diagnoses of motor neuron disease: lessons from the Scottish Motor Neuron Disease Register. *J Neurol Neurosurg Psychiatry* **60:**147–151.

Davies E, Hopkins A (1997). Good practice in the management of adults with malignant cerebral glioma: clinical guidelines. Working Group. *Br J Neurosurg* **11:**318–330.

Dengler R (1999). Current treatment pathways in ALS: a European perspective. *Neurology* **53:**S4–10.

Desport JC, Preux PM, Truong CT, Courat L, Vallat JM, Couratier P (2000). Nutritional assessment and survival in ALS patients. *Amyotroph Lateral Scler Other Motor Neuron Disord* **1:**91–96.

Diener HC, Dethlefsen U, Dethlefsen-Gruber S, Verbeek P (2002). Effectiveness of quinine in treating muscle cramps: a double-blind, placebo-controlled, parallel-group, multicentre trial. *Int J Clin Pract* **56:**243–246.

Dogu O, Apaydin D, Sevim S *et al.* (2004). Ultrasound-guided versus 'blind' intraparotid injections of botulinum toxin-A for the treatment of sialorrhoea in patients with Parkinson's disease. *Clin Neurol Neurosurg* **106:**93–96.

Doyle D (1996). Breaking bad news. *J R Soc Med* **89:**590–591.

Drory VW, Goltsman E, Renik JG *et al.* (2001). The value of muscle exercise in patients with amyotrophic lateral sclerosis. *J Neurol Sci* **191:**133–137.

Evangelista T, Carvalho M, Conceicao I, Pinto A, de Lurdes M, Luis ML (1996). Motor neuropathies mimicking amyotrophic lateral sclerosis/motor neuron disease. *J Neurol Sci* **139**(Suppl.)**:**95–98.

Fong KY, Yu YL, Chan YW *et al.* (1996). Motor neuron disease in Hong Kong Chinese: Epidemiology and clinical picture. *Neuroepidemiology* **15:**239–245.

Forsgren L, Almay BG, Holmgren G, Wall S (1983). Epidemiology of motor neuron disease in northern Sweden. *Acta Neurol Scand* **68:**20–29.

Forshew DA, Bromberg MB (2003). A survey of clinicans' practice in the symptomatic treatment of ALS. *Amyotroph Lateral Scler Other Motor Neuron Disord* **4:**258–263.

Gallagher JP (1989). Pathologic laughter and crying in ALS: a search for their origin. *Acta Neurol Scand* **80:**114–117.

Garcia-Redondo A, Bustos F, Juan Y, Seva B *et al.* (2002). Molecular analysis of the superoxide dismutase 1 gene in Spanish patients with sporadic or familial amyotrophic lateral sclerosis. *Muscle Nerve* **26:**274–278.

*Gasser T, Dichgans M, Finsterer J *et al.* (2001). EFNS task force on molecular diagnosis of neurologic disorders. Part 1. *Eur J Neurol* **8:**299–314.

Gellera C (2001). Genetics of ALS in Italian families. *Amyotroph Lateral Scler Other Motor Neuron Disord* **2**(Suppl. 1)**:**S43–46.

Giagheddu M, Puggioni G, Masala C *et al.* (1983). Epidemiologic study of amyotrophic lateral sclerosis in Sardinia, Italy. *Acta Neurol Scand* **68:**394–404.

Giess R, Naumann M, Werner E *et al.* (2000). Injections of botulinum toxin A into the salivary glands improve sialorrhoea in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* **69:**121–123.

Gunnarsson L-G, Palm R (1984). Motor neuron disease and heavy labour: an epidemiological survey of Värmland county, Sweden. *Neuroepidemiology* **3:**195–206.

Højer-Pedersen E, Christensen PB, Jensen NB (1989). Incidence and prevalence of motor neuron disease in two Danish counties. *Neuroepidemiology* **8:**151–159.

Haberlandt WF (1959). Genetic aspects of amyotrphic lateral sclerosis and progressive bulbar paralysis. *Acta Genet Med Gemellol (Roma)* **8:**369–373.

Hanayama K, Ishikawa Y, Bach JR (1997). Amyotrophic lateral sclerosis: successful treatment of mucous plugging by mechanical insufflation-exsufflation. *Am J Phys Med Rehabil* **76:**338–339.

Harriman M, Morrison M, Hay J *et al.* (2001). Use of radiotherapy for control of sialorrhea in patients with amyotrophic lateral sclerosis. *J Otolaryngol* **30:**242–245.

Haverkamp LJ, Appel V, Appel SH (1995). Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. *Brain* **118:**707–719.

Heffernan C, Jenkinson C, Holmes T *et al.* (2004). Nutritional management in MND/ALS patients: an evidence based review. *Amyotroph Lateral Scler Other Motor Neuron Disord* **5:**72–83.

Hockstein NG, Samadi DS, Gendron K, Handler SD (2004). Sialorrhea: a management challenge. *Am Fam Physician* **69:**2628–2634.

*Howard RS, Orrell RW (2002). Management of motor neurone disease. *Postgrad Med J* **78:**736–741.

Hyson HC, Johnson AM, Jog MS (2002). Sublingual atropine for sialorrhea secondary to parkinsonism: a pilot study. *Mov Disord* **17:**1318–1320.

Iannaccone S, Ferini-Strambi L (1996). Pharmacologic treatment of emotional lability. *Clin Neuropharmacol* **19:**532–535.

Ince PG, Lowe J, Shaw PJ (1998). Amyotrophic lateral sclerosis: current issues in classification, pathogenesis and molecular pathology. *Neuropathol Appl Neurobiol* **24:**104–117.

Jackson M, Al-Chalabi A, Enayat ZE, Chioza B, Leigh PN, Morrison KE (1997). Copper/zinc superoxide dismutase 1 and sporadic amyotrophic lateral sclerosis: analysis of 155 cases and identification of a novel insertion mutation. *Ann Neurol* **42:**803–807.

Janzen VD, Rae RE, Hudson AJ (1988). Otolaryngologic manifestations of ALS. *J Otolaryngology* **17:**41–42.

*Jennings AL, Davies AN, Higgins JP, Gibbs JS, Broadley KE (2002). A systematic review of the use of opioids in the management of dyspnoea. *Thorax* **57:**939–944.

Jokelainen M (1977). Amyotrophic lateral sclerosis in Finland. II: Clinical characteristics. *Acta Neurol Scand* **56:**194–204.

Jones CT, Swingler RJ, Simpson SA, Brock DJ (1995). Superoxide dismutase mutations in an unselected cohort of Scottish amyotrophic lateral sclerosis patients. *J Med Genet* **32:**290–292.

Kesiktas N, Paker N, Erdogan N, Gulsen G, Bicki D, Yilmaz H (2004). The use of hydrotherapy for the management of spasticity. *Neurorehabil Neural Repair* **18:**268–273.

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

Lee JRJ, Annegers JF, Appel S (1995). Prognosis of ALS and the effects of referral selection. *J Neurol Sci* **132:**207–215.

*Leigh PN, Abrahams S, Al-Chalabi A *et al.* (2003). The management of motor neurone disease. *J Neurol Neurosurg Psychiatry* **70**(Suppl. IV)**:**iv32–iv47.

Li TM, Day SJ, Alberman E, Swash M (1986). Differential diagnosis of motoneurone disease from other neurological conditions. *Lancet* **2:**731–733.

Li T-M, Alberman E, Swash M (1988). Comparison of sporadic and familial disease amongst 580 cases of motor neuron disease. *J Neurol Neurosurg Psychiatry* **51:**778–784.

Lima A, Evangelista T, de Carvalho M (2003). Increased creatine kinase and spontaneous activity on electromyography, in amyotrophic lateral sclerosis. *Electromyogr Clin Neurophysiol* **43:**189–192.

Lind SE, Good MD, Seidel S, Csordas T, Good BJ (1989). Telling the diagnosis in cancer. *J Clin Oncol* **7:**583–589.

Lyall RA, Donaldson N, Polkey MI, Leigh PN, Moxham J (2001). Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. *Brain* **124:**2000–2013.

Marquardt G, Seifert V (2002). Use of intrathecal baclofen for treatment of spasticity in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* **72:**275–276.

Mathus-Vliegen LM, Louwerse LS, Merkus MP, Tytgat GN, Vianney de Jong JM (1994). Percutaneous endoscopic gastrostomy in patients with amyotrophic lateral sclerosis and impaired pulmonary function. *Gastrointest Endosc* **40:**463–469.

McCluskey L, Casarett D, Siderowf A (2004). Breaking the news: a survey of ALS patients and their caregivers. *Amyotroph Lateral Scler Other Motor Neuron Disord* **5:**131–135.

Meininger V (1999). Getting the diagnosis right: beyond El Escorial. *J Neurol* **246**(Suppl. 3)**:**III10–III15.

Mier RJ, Bachrach SJ, Lakin RC, Barker T, Childs J, Moran M (2000). Treatment of sialorrhea with glycopyrrolate: a double-blind, dose-ranging study. *Arch Pediatr Adolesc Med* **154:**1214–1218.

Miller RG (2001). Examining the evidence about treatment in ALS/MND. *Amyotroph Lateral Scler Other Motor Neuron Disord* **2:**3–7.

*Miller RG, Rosenberg JA, Gelinas DF *et al*. (1999). 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: ALS Practice Parameters Task Force. *Neurology* **52:**1311–1323.

Miller RG, Mitchell JD, Lyon M, Moore DH (2002). Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* (2):CD001447.

Murphy J (2004). Communication strategies of people with ALS and their partners. *Amyotroph Lateral Scler Other Motor Neuron Disord* **5:**121–126.

Murray TJ, Pride S, Haley G (1974). Motor neuron disease in Nova Scotia. *CMAJ* **110:**814–817.

Murros K, Fogelholm R (1983). Amyotrophic lateral sclerosis in middle-Finland: an epidemiological study. *Acta Neurol Scand* **67:**41–47.

Newall AR, Orser R, Hunt M (1996). The control of oral secretions in bulbar ALS/MND. *J Neurol Sci* **139**(Suppl.)**:**43–44.

Niemann S, Joos H, Meyer T *et al*. (2004). Familial ALS in Germany: origin of the R115G SOD1 mutation by a founder effect. *J Neurol Neurosurg Psychiatry* **75:**1186–1188.

Norris FH Jr, U KS, Sachais B, Carey M. (1979). Trial of baclofen in amyotrophic lateral sclerosis. *Arch Neurol* **36:**715–716.

Oliver D, Borasio GD, Walsh D, eds. (2000). *Palliative Care in Amyotrophic Lateral Sclerosis*. Oxford University Press, Oxford.

Orrell RW, Habgood JJ, Gardiner I *et al*. (1997). Clinical and functional investigation of 10 missense mutations and a novel frameshift insertion mutation of the gene for copper-zinc superoxide dismutase in UK families with amyotrophic lateral sclerosis. *Neurology* **48:**746–751.

Poeck K (1996). Pathologisches lachen und weinen bei bulber amyotrophischer lateralsklerose. *Dtsch Med Wochenschr* **94:**310–314.

Porta M, Gamba M, Bertacchi G, Vaj P (2001). Treatment of sialorrhoea with ultrasound guided botulinum toxin A injection in patients with neurological disorders. *J Neurol Neurosurg Psychiatry* **70:**538–540.

Rosen AD (1978). Amyotrophic lateral sclerosis. Clinical features and prognosis. *Arch Neurol* **35:**638–642.

Ross MA, Miller RG, Berchert L *et al*. (1998). Towards earlier diagnosis of ALS. Revised criteria. *Neurology* **50:**768–772.

Sancho J, Servera E, Diaz J, Marin J (2004). Efficacy of mechanical insufflation-exsufflation in medically stable patients with amyotrophic lateral sclerosis. *Chest* **125:**1400–1405.

dos Santos MT, de Oliveira LM (2004). Use of cryotherapy to enhance mouth opening in patients with cerebral palsy. *Spec Care Dentist* **24:**232–234.

Schiffer RB, Herndon RM, Rudick RA (1985). Treatment of pathological laughing and weeping with amitriptyline. *N Engl J Med* **312:**1480–1482.

Scott AG, Austin HE (1994). Nasogastric feeding in the management of severe dysphagia in motor neurone disease. *Palliat Med* **8:**45–49.

Shaw CE, Enayat ZE, Chioza BA *et al*. (1998). Mutations in all five exons of SOD-1 may cause ALS. *Ann Neurol* **43:**390–394.

Shaw AS, Ampong MA, Rio A, McClure J, Leigh PN, Sidhu PS (2004). Entristar skin-level gastrostomy tube: primary placement with radiologic guidance in patients with amyotrophic lateral sclerosis. *Radiology* **233:**392–399.

Stalpers LJ, Moser EC (2002). Results of radiotherapy for drooling in amyotrophic lateral sclerosis. *Neurology* **58:**1308.

Sykes N, Thorns A (2003). The use of opioids and sedatives at the end of life. *Lancet Oncol* **4:**312–318.

Talmi YP, Finkelstein Y, Zohar Y (1989). Reduction of salivary flow in amyotrophic lateral sclerosis with Scopoderm TTS. *Head Neck* **11:**565.

Talmi YP, Finkelstein Y, Zohar Y. (1990). Reduction of salivary flow with transdermal scopolamine: a four-year experience. *Otolaryngol Head Neck Surg* **103:**615–618.

Tan EK, Lo YL, Seah A, Auchus AP (2001). Recurrent jaw dislocation after botulinum toxin treatment for sialorrhoea in amyotrophic lateral sclerosis. *J Neurol Sci* **190:**95–97.

Thijs V, Peeters E, Theys P, Matthijs G, Robberecht W (2000). Demographic characteristics and prognosis in a Flemish amyotrophic lateral sclerosis population. *Acta Neurol Belg* **100:**84–90.

Thornton FJ, Fotheringham T, Alexander M, Hardiman O, McGrath FP, Lee MJ (2002). Amyotrophic lateral sclerosis: enteral nutrition provision–endoscopic or radiologic gastrostomy? *Radiology* **224:**713–717.

Traynor BJ, Codd MB, Corr B, Forde C, Frost E, Hardiman O (2000). Amyotrophic Lateral sclerosis mimic syndromes. *Arch Neurol* **57:**109–113.

Traynor BJ, Alexander M, Corr B *et al*. (2003a). Effects of a multidisciplinary ALS clinic on survival. *J Neurol Neurosurg Psychiatry* **74:**1258–1261.

Traynor BJ, Alexander M, Corr B, Frost E, Hardiman O (2003b). An outcome study of riluzole in amyotrophic lateral sclerosis – a population-based study in Ireland, 1996–2000. *J Neurol* **250:**473–479.

Turner MR, Bakker M, Sham P, Shaw CE, Leigh PN, Al-Chalabi A (2002). Prognostic modelling of therapeutic interventions in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* **3:**15–21.

Wilbourn AJ (1998). Clinical neurophysiology in the diagnosis of amyotrophic lateral sclerosis: the Lambert and the El Escorial criteria. *J Neurol Sci* **160**(Suppl. 1)**:**S25–29.

Winterholler MG, Erbguth FJ, Wolf S, Kat S (2001). Botulinum toxin for the treatment of sialorrhoea in ALS: serious side effects of a transductal approach. *J Neurol Neurosurg Psychiatry* **70:**417–418.

Winterholler MG, Heckmann JG, Hecht M, Erbguth FJ (2002). Recurrent trismus and stridor in an ALS patient: successful treatment with botulinum toxin. *Neurology* **58:**502–503.