Amyotrophic lateral sclerosis
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Amyotrophic lateral sclerosis (known in the UK as motor neuron disease) is a devastating illness for patients, relatives, and carers. It is also one of the most puzzling diseases in medicine in terms of our understanding of its pathogenesis.

**Natural history, clinical features, and epidemiology**

**Natural history**

Amyotrophic lateral sclerosis is one of the major neurodegenerative diseases alongside Alzheimer’s disease and Parkinson’s disease. It is a progressive disorder that involves degeneration of the motor system at all levels. Involvement of other elements of the nervous system has been described, particularly at post mortem, but motor system involvement is most important in relation to clinical features noted during life. Overlap with other neurodegenerative diseases is sometimes seen; some patients have associated frontotemporal dementia.

**Clinical features**

The clinical features of amyotrophic lateral sclerosis are indicative of the loss of neurons at all levels of the motor system—from the cortex to the anterior horn of the spinal cord. Physical signs of this disorder thus encompass both upper motor neuron and lower motor neuron findings. Objective sensory findings are incompatible with a diagnosis of amyotrophic lateral sclerosis unless they can be accounted for by neurological comorbidity. The course of the disorder is inexorably progressive, with 50% of patients dying within 3 years of onset. The clinical features can be considered in relation to neurological regions or levels: bulbar, cervical, and lumbar. A fourth thoracic level is sometimes mentioned but is rarely an issue in routine clinical practice, except in relation to paraspinus electromyography (EMG).

Bulbar-onset patients present with slurring of speech (dysarthria), difficulty swallowing (dysphagia), or both. Exclusion of other potentially treatable diseases is important—e.g., oesophageal carcinoma and myasthenia gravis. Bulbar involvement can be lower motor neuron (bulbar palsy), upper motor neuron (pseudobulbar palsy), or both. Bulbar palsy is associated with upper and lower facial weakness and poverty of palatal movement with wasting, weakness, and fasciculation of the tongue. Pseudobulbar palsy is characterised by emotional lability (also known as pathological laughing or crying), brisk jaw jerk, and dysarthria.

Cervical-onset amyotrophic lateral sclerosis presents with upper-limb symptoms, either bilateral or unilateral. Proximal weakness can present as difficulty with tasks associated with shoulder abduction (eg, hair washing, combing, etc), and distal weakness can manifest with impairment of activities requiring pincer grip. Upper limb signs might also be upper motor neuron, lower motor neuron, or both. The arm can be strikingly wasted with prefrontal fasciculation and brisk reflexes.

Lumbar onset implies degeneration of the anterior horn cells of the lumbar enlargement and is associated with lower motor neuron symptoms and signs in the legs, such as a tendency to trip (foot drop) or difficulty on stairs (proximal weakness).

**Search strategy and selection criteria**

The literature search was aimed at finding papers relevant to this Seminar dating back to 2000. Medline and Embase were used as the basis of this search. Papers relating to amyotrophic lateral sclerosis were sought with the terms: “ALS”, “MND”, “amyotrophic lateral sclerosis”, “motor neuron disease”, and “motor neuron disease”. Papers on motor neuron disease identified with this strategy were further selected for relevance by seeking those containing the following terms: “epidemiology”, “natural history”, “management”, “dysphagia”, “salivary gland”, “nucleolus”, “pain”, “depression”, “ventilation”, “symptom control”, “psychosocial care”, “spinal care”, “palliative care”, “stem cells”, “excitotoxicity”, “glutamate”, “superoxide”, and “familial”. Additional papers—some from before 2000—known to us through our knowledge of published work relating to amyotrophic lateral sclerosis were included when judged appropriate.
**Variant syndromes**

Progressive muscular atrophy is a lower motor neuron syndrome without upper motor neuron signs. The relation between progressive muscular atrophy and amyotrophic lateral sclerosis has been debated extensively. Some patients with progressive muscular atrophy progress fairly slowly, prompting the suggestion that the disorder is a variant of spinal muscular atrophy, a much less aggressive motor neuron disease. Other affected individuals presenting with progressive muscular atrophy eventually develop full amyotrophic lateral sclerosis.

Conversely, primary lateral sclerosis is a pure upper motor neuron disease without lower motor neuron involvement. This entity has also been debated widely. In a review of 39 patients with primary lateral sclerosis, 16 remained free of lower motor neuron signs throughout their clinical course but 13 eventually presented with evidence of lower motor neuron involvement, suggesting that a substantial proportion of these individuals develop amyotrophic lateral sclerosis before death.

**Mimic syndromes**

Slow progression and absence of upper motor neuron signs strongly suggest mimic syndromes. Although technically a variant of spinal muscular atrophy, bulbar muscular atrophy (Kennedy's syndrome)—an X-linked recessive lower motor neuron syndrome with bulbar involvement—can be confused with amyotrophic lateral sclerosis. Tongue wasting and fasciculation, gynaecomastia, testicular atrophy, and infertility are characteristic findings. Some patients also have a primary sensory neuropathy. Kennedy's syndrome links to Xq11-q12 and is associated with a CAG repeat sequence in the androgen receptor gene.

Multifocal motor neuropathy is an important differential diagnosis because it is potentially treatable. Weakness generally affects distal arm muscles and can be in the distribution of individual nerves. Cranial nerves and respiratory muscles are rarely affected. Upper motor neuron signs are absent and the disease can be very slowly progressive, over a period of up to 30 years. The neurophysiological hallmark is the finding of conduction blocks. IgM anti-GM1 ganglioside antibodies are frequently positive. Great improvement with immunomodulatory treatment can take place even in patients with severe weakness. Intravenous immunoglobulin is usually the first treatment of choice. Some researchers also suggest benefit from cyclophosphamide, but a high risk of serious adverse events is present with this drug. Findings of Cochrane systematic reviews have not recorded clear evidence from randomised controlled trials of the best treatment. Use of corticosteroids has been associated with deterioration. Little or no evidence is available about drugs less toxic than cyclophosphamide, such as azathioprine, interferon beta, rituximab, ciclosporin, and plasma exchange.

**Epidemiology and genetic forms**

The incidence of sporadic amyotrophic lateral sclerosis is between 1.5 and 2.0 per 100,000 population per year, giving a prevalence of around 6 per 100,000. Males are usually affected more than females (ratio about 1:6:1). Areas with an apparently higher prevalence of an amyotrophic lateral sclerosis-like disease compared with other regions—notably around the Pacific rim (eg, Guam)—have long been a source of interest to epidemiologists. The role of methylmalonic aciduria in these foci is of particular interest. Research suggests a cyanobacterial origin for methylmalonic aciduria in cyanidic tissue with resultant biomagnification in the food chain. The traditional diet of the Chamorro population, who live on the Pacific island of Guam, includes the fruit bat, which feeds on cyanidic seeds and has been reported to bioaccumulate methylmalonic acid.

<table>
<thead>
<tr>
<th>Designation</th>
<th>Locus</th>
<th>Gene</th>
<th>Inheritance</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS 1</td>
<td>2q21</td>
<td>Copper/zinc superoxide dismutase (SOD1)</td>
<td>Autosomal dominant</td>
<td>Many (about 100) mutations now described</td>
</tr>
<tr>
<td>ALS 2</td>
<td>3q33</td>
<td>ALS: a guanine nucleotide exchange factor for RAB5A, a key regulator of endocytosis</td>
<td>Autosomal recessive</td>
<td>Upper motor neuron features might be prominent</td>
</tr>
<tr>
<td>ALS 3</td>
<td>18q21</td>
<td>Not known</td>
<td>Autosomal dominant</td>
<td></td>
</tr>
<tr>
<td>ALS 4</td>
<td>9q34</td>
<td>Sensine (SETF2); could have RNA and DNA helicase activities and act in DNA repair pathways</td>
<td>Autosomal dominant</td>
<td>Onset age might be younger than 25 years, slow progression, normal lifespan?</td>
</tr>
<tr>
<td>ALS 5</td>
<td>15q15.1-q21.1</td>
<td>Not known</td>
<td>Autosomal recessive</td>
<td></td>
</tr>
<tr>
<td>ALS 6</td>
<td>18q12.1-q12.2</td>
<td>Not known</td>
<td>Autosomal dominant</td>
<td></td>
</tr>
<tr>
<td>ALS 7</td>
<td>20pter</td>
<td>Not known</td>
<td>Autosomal dominant</td>
<td></td>
</tr>
<tr>
<td>ALS 8</td>
<td>20q13.3</td>
<td>Vesicle-associated membrane protein/synaptobrevin-associated membrane protein 8 (VAP8) gene</td>
<td>Autosomal dominant</td>
<td>Possible founder effect</td>
</tr>
<tr>
<td>Lower motor neuron disease, distal type</td>
<td>2p13</td>
<td>Dynein 1 gene (DCTRI)</td>
<td>Autosomal dominant</td>
<td>Very slowly progressive, upper motor neuron signs only</td>
</tr>
</tbody>
</table>

Table 1: Summary of familial amyotrophic lateral sclerosis variants
Increased age of onset, low forced vital capacity, short time from first symptom to presentation, and bulbar onset are all adverse prognostic indicators. A host of environmental factors have been investigated as potential risk factors for amyotrophic lateral sclerosis. Unfortunately, many studies to date have been insufficiently powered. Putative physical and toxic risk factors have also been reviewed, again without any clear pointers emerging. Substantially raised risks of developing amyotrophic lateral sclerosis have been reported in Italian professional football players. Increased risks have also been suggested in military personnel. Although potential associations between amyotrophic lateral sclerosis and smoking have been discussed, evidence for this link remains unclear.

5–10% of patients have a positive family history for amyotrophic lateral sclerosis. These kindreds usually show an autosomal-dominant pattern of inheritance. Autosomal-recessive forms have also been described, particularly from highly consanguineous populations in north Africa. Between 10% and 20% of autosomal-dominant patients have mutations in the copper/zinc superoxide dismutase (SOD1) gene on chromosome 21. Other linkages have also been reported in people with familial amyotrophic lateral sclerosis but the genetic lesion in most of these affected individuals remains unknown. Table 1 summarises potential variants and linkages of the familial disorder. Additionally, several other genetic factors have been reported to alter the risk of developing sporadic amyotrophic lateral sclerosis. These include angiotensin (14q11.2), vascular endothelial growth factor (6p12), survival motor neuron (5q12.2–q13.3), neurofilament protein (22q12.2), and charged multivesicular body protein 28 (2p11.2).  

### Diagnostic criteria, clinical rating scales, and quality-of-life measurement

The El Escorial diagnostic criteria for amyotrophic lateral sclerosis were developed in the late 1980s and have subsequently been revised. Panel 1 shows the essential features of the revised criteria. Although intended as an aid to research and slightly more restrictive than the burden of proof usually applied in clinical practice, these criteria do provide a structured approach to assessment of people suspected of having amyotrophic lateral sclerosis, which can enhance objectivity in clinical practice and facilitate clinical studies. Several functional rating scales have also been developed over the past 20–25 years. These include the Norris scale, the Appel amyotrophic lateral sclerosis rating scale, and the amyotrophic lateral sclerosis functional rating scale. This latter scale is, at present, the most widely used in clinical trials. Many assessment scales have been used to measure quality of life in the broad sense in individuals with amyotrophic lateral sclerosis. Most are actually designed to assess general or disease-specific health status, such as the short form 36 or the amyotrophic lateral sclerosis specific questionnaires, the ALSAQ 40, and thus they correlate well with functional rating scales. However, patients with amyotrophic lateral sclerosis seem to prefer individual quality-of-life scales, such as the schedule for evaluation of individual quality of life-direct weighting. Individual quality of life is dependent on factors other than physical functioning and does not necessarily deteriorate, despite progressing disability.

### Causal and pathogenetic hypotheses

Many causal and pathogenetic hypotheses for amyotrophic lateral sclerosis have been proposed over the years, ranging from heavy-metal toxic effects to environmental and occupational exposures. Despite extensive research, the disorder remains poorly understood in terms of a unifying causal hypothesis and, indeed, might turn out to be a common end-stage phenotype of diverse causes. Current work focuses largely on excitotoxicity and oxidant stress. Viral hypotheses drawing from the role of poliovirus in poliomyelitis have been pursued extensively without positive evidence emerging. Excitotoxicity is the process by which aminos isomeric neurotransmitters such as glutamate become toxic when present at supraphysiological concentrations. Other potential excitotoxins include AMPA (α-amino-hydroxy-5-methylisoxazole-4-propionic acid) and kainate. Excitotoxins are thought to precipitate neuronal death by triggering excessive calcium influx into the motor neuron, which is mediated at membrane level, and stimulating an intraneuronal cascade mechanism including free-radical intermediates, ultimately resulting
in neuronal death. The excitotoxic and free-radical theories are, thus, not mutually exclusive. The excitotoxic hypothesis has led to the identification of riluzole, a glutamate-release inhibitor, as the first licensed disease-modifying treatment for amyotrophic lateral sclerosis. Attempts to develop antioxidant strategies for the disorder have, by contrast, been disappointing. Other pathogenetic hypotheses have centred on dysregulation of intracellular calcium, axonal transport defects, and protein aggregation.

Early investigations seeking a potential role for free radicals in the pathogenesis of amyotrophic lateral sclerosis became much more tightly focused after Rosen published his report of the chromosome 21 SOD1 gene mutation in some families with a history of familial amyotrophic lateral sclerosis. This mutation has since been recorded in individuals with apparently sporadic disease, but some of these patients were subsequently shown to be related in a much earlier generation (common founder effect). Although more than 10 years have elapsed since Rosen’s paper, the link between the SOD1 gene mutation and amyotrophic lateral sclerosis remains unclear. Copper chaperone proteins have been discussed in this context, and the putative toxic gain of function of mutant SOD1 remains elusive despite intense research. Whether neuronal death in amyotrophic lateral sclerosis is due to apoptosis is also still a matter of debate. Two essential issues that need to be remembered are: 1) SOD1 is associated with no more than 20% of total cases of familial amyotrophic lateral sclerosis, and the familial disease only accounts for 5–10% of amyotrophic lateral sclerosis cases; and 2) the mutant SOD1 enzyme is expressed in all tissues from birth to death. Why do people with SOD1 gene mutations live a substantial proportion of their normal lifespan (generally >60%) as apparently healthy individuals before they develop a catastrophic degenerative disorder affecting a very specific neuronal population, which will result in

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Dose and route</th>
<th>Trial design</th>
<th>Status/outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEC1-10150</td>
<td>Antioxidant</td>
<td>Not known, subcutaneous</td>
<td>Not known</td>
<td>Phase 1 clinical trials, pivotal phase II/III trials planned</td>
</tr>
<tr>
<td>Brain-derived</td>
<td>Neurotrophin</td>
<td>25 or 100 μg/kg</td>
<td>Randomised, placebo-controlled, dose-ranging trial</td>
<td>Failed to show benefit for primary endpoints</td>
</tr>
<tr>
<td>neurotrophic</td>
<td>(BDNF)</td>
<td>25, 60, 150, 400, or</td>
<td>Randomised, double-blind, sequential, dose-escalation study</td>
<td></td>
</tr>
<tr>
<td>factor (BDNF)</td>
<td></td>
<td>1000 μg/kg, intrathecal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciliary</td>
<td>Neurotrophin</td>
<td>0.5, 2, or 5 μg/kg/day</td>
<td>Double-blind, placebo-controlled, dose-ranging trial</td>
<td>No beneficial effect on progression; adverse events and deaths increased in 5 μg/kg group</td>
</tr>
<tr>
<td>neurotrophic</td>
<td></td>
<td>3 or 30 μg/kg, subcutaneous</td>
<td>Randomised, placebo-controlled, dose-ranging, double-blind trial</td>
<td>No significant difference between CNTF and placebo; side-effects sufficient to limit use in many cases</td>
</tr>
<tr>
<td>factor (CNTF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatine</td>
<td>Stabilise</td>
<td>500 mg/day</td>
<td>Double-blind, placebo-controlled, sequential</td>
<td>Did not have a beneficial effect on survival or disease progression</td>
</tr>
<tr>
<td></td>
<td>mitochondrial</td>
<td></td>
<td>trial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Antiepileptic</td>
<td>-</td>
<td>Randomised, placebo-controlled trial</td>
<td>No evidence of beneficial effect on disease progression</td>
</tr>
<tr>
<td></td>
<td>agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamine</td>
<td>Immunosuppressant</td>
<td>-</td>
<td>Randomised controlled trial</td>
<td>Status uncertain, further studies needed</td>
</tr>
<tr>
<td>Glaxosine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon beta</td>
<td>Immunomodulatory</td>
<td>12 μL, subcutaneously, three times a week</td>
<td>Randomised, placebo-controlled trial</td>
<td>The results of this pilot study suggest that interferon beta 1A is not effective</td>
</tr>
<tr>
<td>Interferon beta</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Glutamate release</td>
<td>300 mg/day, oral</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>No evidence of effectiveness</td>
</tr>
<tr>
<td></td>
<td>inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minocycline</td>
<td>Inhibits glutamate</td>
<td>Up to 400 mg/day, oral</td>
<td>Compounded, with and without riluzole</td>
<td>Status not yet clear; further trials planned</td>
</tr>
<tr>
<td></td>
<td>release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ONO 1556 (Cerepe)</td>
<td>Antioxidant</td>
<td>1-2 g/day, oral</td>
<td>Compounded, with and without riluzole</td>
<td>Results pending</td>
</tr>
<tr>
<td>Pentoxifyline</td>
<td>Tumour necrosis factor</td>
<td>1-2 g/day, oral</td>
<td>Double-blind, randomised, placebo-controlled, multicentre trial</td>
<td>Not beneficial and should be avoided in patients treated with riluzole</td>
</tr>
<tr>
<td>Recombinant IGF-I</td>
<td>Neurotrophin</td>
<td>0.65 and 0.4 mg/kg per day</td>
<td>Placebo-controlled dose-ranging trial</td>
<td>Interpretation of trial results, jeopardised by trial design, further studies in progress</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Glutamate release</td>
<td>300 mg/day, oral</td>
<td>Double-blind, placebo-controlled, dose-ranging</td>
<td>Modesty effective</td>
</tr>
<tr>
<td></td>
<td>inhibitor</td>
<td></td>
<td>trial</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Antiepileptic</td>
<td>Up to 800 mg/day, oral</td>
<td>Placebo-controlled dose-ranging trial</td>
<td>Did not alter decline in forced vital capacity and amyotrophic lateral sclerosis functional rating scale and affect survival; further studies of topiramate up to 800 mg/day are not warranted</td>
</tr>
<tr>
<td>Xaliprofen</td>
<td>Antioxidant</td>
<td>1 and 2 mg/day, oral</td>
<td>Randomised, placebo-controlled trial</td>
<td>No evidence of effect on survival or motor function</td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
<td>α-tocopherol (500 mg twice a day)</td>
<td>Randomised, placebo-controlled trial</td>
<td>No evidence of effectiveness</td>
</tr>
</tbody>
</table>

Table 3: Some putative disease-modifying treatments for amyotrophic lateral sclerosis
death within less than 5% of the typical lifespan. One possible answer could reside in the notion of selective motor neuron vulnerability, which might be related to a reduced amount of calcium-binding proteins in motor neurons, although the size of the motor neuron and resultant energy requirements, length of the motor neuronalaxon, and molecular profile of glutamate receptors might also be important. Identification of TDP43 as the major ubiquitinated protein in both frontotemporal dementia and sporadic amyotrophic lateral sclerosis suggests a range of disorders with similar pathological mechanisms, culminating in the progressive degeneration of different selectively vulnerable neurons.

Management
Disease-modifying treatments
Many putative disease-modifying strategies for amyotrophic lateral sclerosis have been tested in clinical trials (table 2), but only one drug (riluzole) has so far been licensed. One of the actions of riluzole is as a glutamate-release inhibitor acting on sodium channels. In this context, riluzole has similar pharmacological properties to lamotrigine. It prolongs the lifespan of patients with amyotrophic lateral sclerosis by an average of 3 months. Findings of an initial trial in individuals with this disorder suggested that riluzole was more effective in bulbar-onset than limb-onset patients. This result was not repeated in a second, larger, dose-ranging trial. After publication of a Cochrane systematic review and an assessment by the UK's National Institute for Clinical Excellence, further studies were recommended to investigate aspects of the potential effectiveness of riluzole in amyotrophic lateral sclerosis. This work has not yet been done but some observational surveys and audit data for the so-called real-world clinical use of riluzole have been reported, which suggest a longer survival time than that recorded in randomised controlled trials, a finding that needs confirmation.

Nerve growth factors (neurotrophins) have also been investigated as disease-modifying treatments for amyotrophic lateral sclerosis. Neurotrophins are thought to have a key role in maintenance of neuronal viability, prompting suggestions that they might be able to rescue dying motor neurons.

Recombinant insulin-like nerve growth factor 1 is a naturally occurring peptide with multigene neurotrophic potential on motor neurons. Two randomised placebo-controlled trials of this peptide in patients with amyotrophic lateral sclerosis have been completed to date, which were seriously compromised by flawed trial design. A Cochrane review has been undertaken, and the effectiveness of recombinant insulin-like nerve growth factor 1 for treatment of this disorder remains unproven, although the drug might be modestly effective. Hopefully, a current trial in North America will provide new insights into the effectiveness of this peptide in amyotrophic lateral sclerosis.

Ciliary neurotrophic factor and brain-derived neurotrophic factor have both shown promising results in vitro and in animal models. However, findings of clinical trials with parenteral and (for brain-derived neurotrophic factor) intrathecal administration have been disappointing (table 2).

Symptom control and palliative care
Palliative care for patients with amyotrophic lateral sclerosis, which includes all measures aimed at relief of symptoms and improvement of quality of life, starts with communication of diagnosis and goes all the way to bereavement counselling (figure). Panel 2 includes all the main symptoms of the disorder. Despite first attempts at establishing evidence-based guidelines, standards of palliative treatment in patients with amyotrophic lateral sclerosis are still largely based on expert opinion and differ between countries. If possible, affected individuals should be referred to the closest multidisciplinary clinic for amyotrophic lateral sclerosis. Early cooperation between the treating doctor and the local palliative care or hospice team can be of invaluable help for patients and families.

Communicating a diagnosis of amyotrophic lateral sclerosis is one of the most important tasks for the doctor. Callosum delivery of the diagnosis can be detrimental to the therapeutic relationship and might negatively affect psychological adjustment to bereavement. The patient should dictate the pace and depth of the information flow and the doctor has the task of responding appropriately to the patient's cues. The issue of complementary treatments should be discussed proactively.

At onset of symptoms of dyspnoea or chronic nocturnal hypoventilation, or when forced vital capacity drops below 50%, the patient should be offered information

![Figure: Course of palliative care in amyotrophic lateral sclerosis](image-url)
Panel 2: Symptoms attributable to amyotrophic lateral sclerosis

Direct (owing to motor neuronal degeneration)
- Weakness and atrophy
- Fasciculations and muscle cramps
- Spasticity
- Dysarthria
- Dysphagia
- Dyspnoea
- Emotional lability

Indirect (as a result of primary symptoms)
- Psychological disturbances
- Sleep disturbances
- Constipation
- Drooling
- Thick mucus secretions
- Symptoms of chronic hypoventilation
- Pain

about the terminal phase, since at this point most people worry that they will choke to death. This fear can be relieved by describing the mechanism of terminal hypercapnic coma and the resultant peaceful death during sleep. At the same time, affected individuals should be asked about their wishes in the event of a terminal respiratory failure. Since a tracheostomy can result eventually in a so-called locked-in syndrome and death on an intensive-care unit, most patients will usually refuse it. This refusal should be incorporated into an advance directive, which should be reviewed at appropriate intervals because preferences of patients with amyotrophic lateral sclerosis for life-sustaining treatments can change over time.

Control of dysphagia requires an adjustment in diet consistency (recipe books for patients with amyotrophic lateral sclerosis are available from several lay associations). Specific swallowing techniques can help to prevent aspiration. When oral food intake becomes intolerable because of choking, percutaneous endoscopic gastrostomy should be undertaken. In patients with a forced vital capacity less than 50%, gastrostomy placement should be done after institution of non-invasive ventilation because of the increased risk of respiratory insufficiency. Alternatively, a radiologically inserted gastrostomy can be considered.

Dysarthria can lead to complete loss of oral communication. Speech therapy is helpful initially if progression is slow. Modern computer technology can enable even quadriplegic patients to communicate effectively. First attempts at directly exploiting brain electric currents to control computers have shown encouraging results.

Dyspnoea can be a very distressing symptom in patients with amyotrophic lateral sclerosis and most affected individuals die from respiratory failure. Dyspnoic attacks usually have a pronounced anxiety component and are best managed by short-acting benzodiazepines (lorazepam sublingual 0.5–1.0 mg). Particularly in chronic dyspnoea, the feeling of shortness of breath is best treated with morphine (start with 2.5–5.0 mg orally or 1–2 mg subcutaneously or intravenously every 4 h). Titration of the morphine dose against the clinical effect will almost never lead to life-threatening respiratory depression.

Symptoms of chronic nocturnal hypoventilation, such as disordered sleep and daytime fatigue, can arise months to years before terminal respiratory failure and greatly reduce quality of life. Non-invasive ventilation is an efficient and cost-effective palliative measure for these symptoms. Difficulties with mechanical ventilation are usually not related to cost or technical issues but to increasing care needs of patients. Slow progression, good communication skills, mild bulbar involvement, strong motivation on the patient's part, and a supportive family environment are factors that argue in favour of initiation of non-invasive ventilation. To be effective, this strategy needs to be administered for at least 4 h a day, preferably at night. If a patient requests discontinuation of this ventilation treatment, the doctor has a legal and ethical duty to honour the request and to provide appropriate drugs such as morphine and benzodiazepines, to prevent dyspnoea and to ensure a peaceful death.

Thick mucus secretions, which result from a combination of diminished fluid intake and reduced coughing pressure, are difficult to treat. N-acetylcysteine is useful in some cases. Suction is usually not fully effective unless done via a tracheostomy. Manually assisted coughing techniques and mechanical insufflation-exsufflation can both be of help.

Most patients with amyotrophic lateral sclerosis undergo a phase of reactive depression after their diagnosis and need counselling. Full-blown major depression is infrequent (around 10%) but self-reported depressive symptoms arise in 44–75% of affected individuals. Clinically significant depression should be looked for and treated at all disease stages. Selective serotonin reuptake inhibitors are most frequently used; however, amitriptyline has its advantages in amyotrophic lateral sclerosis because it might exert favourable effects on other symptoms such as drooling, emotional lability, and sleep disturbance. Since concordance of depression and distress levels between patients and caregivers is high, attention to the mental health of the caregiver can alleviate the patient's distress as well.

Pathological laughing or crying happens in up to 50% of patients. It is not a mood disorder but rather an abnormal display of affect, which can be very disturbing in social situations. The symptom responds well to drugs (table 3). A combination of dextromethorphan and quinidine has been shown to be effective in a randomised study, but further research on the long-term side-effects and tolerability are needed.
Other symptoms of amyotrophic lateral sclerosis that can be relieved by appropriate drugs include muscle cramps, fasciculations, spasticity, and drooling. Table 3 shows treatment options. The dose of antispasticity drugs needs to be titrated against clinical effect, since a moderate degree of spasticity is usually better for mobility than a fully flaccid paresis. For patients with drooling refractory to treatments listed in table 3, botulinum toxin injections or irradiation of the salivary glands can be considered.

Up to 73% of patients with amyotrophic lateral sclerosis complain of pain. Musculoskeletal pain typically arises in the later stages of the disease due to atrophy and altered tone around joints. Furthermore, muscle contractures and joint stiffness (eg, frozen shoulder) can be painful. Treatment includes physiotherapy, non-steroidal anti-inflammatory drugs, and opioids. Skin pressure pain due to immobility needs special attention by nursing care.

### Psychosocial care

According to US data, many patients with amyotrophic lateral sclerosis show an interest in physician-assisted suicide. Although suicidal actions are fairly rare in people with this disorder, 20% of affected individuals in the Netherlands have died through active euthanasia or physician-assisted suicide. Assessment of patients for hopelessness and early institution of non-pharmacological interventions aimed at maintaining hope and a sense of meaning in life is probably the best way to prevent wishes for hastened death.

When asked about the most important aspects of their quality of life, 100% of people with amyotrophic lateral sclerosis mentioned their family. The burden of care on relatives sometimes exceeds that of the patients and deserves particular attention. Patients’ associations can provide invaluable help and assistance.

### Spiritual care and bereavement

The importance of spiritual care is usually underestimated. Findings of a study suggested that spirituality or religiousness might affect use of percutaneous endoscopic gastrostomy and non-invasive ventilation in patients with amyotrophic lateral sclerosis, and spiritual care can be a source of comfort to affected individuals.

Spiritual care should encompass the whole family as a means of preventing complicated bereavement.

### Terminal phase

In a retrospective survey of 171 patients with amyotrophic lateral sclerosis, more than 90% died peacefully, mostly in their sleep, and none choked to death. Without mechanical ventilation, the death process usually begins with the individual slipping from sleep into coma due to increasing hypercapnia. Restlessness or signs of dyspnoea should be treated with morphine (beginning with 2.5–5.0 mg orally or 1–2 mg subcutaneously or intravenously every 4 h). Oxygen should be administered only if symptomatic hypoxia is recorded. If anxiety is present or suspected it should be treated with lorazepam sublingual (beginning with 1.0–2.5 mg) or midazolam orally or subcutaneously (starting at 1–2 mg). The dose should be increased until satisfactory symptom control is achieved. According to the findings of a meta-analysis, there is virtually no risk of shortening life with these measures.

### Future prospects

**Diagnostic markers and markers of disease progression**

Although there is still no strongly effective disease-modifying treatment for amyotrophic lateral sclerosis, the flow of potential drugs continues. Thus, a methodology that permits rapid testing of new potential treatments, including markers of disease progression, is needed. Spirometry is an important measure that can be used to assess rate of progression in clinical trials of amyotrophic lateral sclerosis, but the reliability of this test is uncertain particularly in patients with prominent bulbar involvement. Sniff nasal pressure is currently being assessed as an alternative. Maximum voluntary isometric contraction has been investigated as a better way to achieve objective measurement of muscle strength than hand-held myometry. However, only fit patients can...
be tested with this method and it is dependent on observer training. Strategies to establish the number of surviving motor units include motor unit number estimation and the neurophysiological index. The methodology needed for motor unit number estimation can be time consuming and the calculation complex, whereas the neurophysiological index is easily calculated from standard data obtained when calculating motor conduction velocity. Potential methods of detecting and quantifying subclinical upper motor neuron involvement, such as transcranial magnetic stimulation and tractography, a magnetic resonance-based strategy encompassing diffusion tensor-weighted imaging technology, have also been discussed as possible progression markers for clinical trials.

Novel methods of delivery of putative disease-modifying treatments

A recurring theme in the discussion of potential disease-modifying treatments for amyotrophic lateral sclerosis is the need to ensure that the investigational substance is delivered to the site of the disease process—ie, the motor neuron—as efficiently as possible. This targeting might not be achieved with oral treatments or parenteral administration. Adenosynovial virus expressing IGF-1 has been used as a means of delivering IGF-1 to motor neurons by injecting the virus into respiratory and limb muscles in G93A SOD1 transgenic mice. This strategy has been reported to prolong survival in this mouse model even if treatment was started after the animals had developed clinical features of amyotrophic lateral sclerosis. Similarly, one injection of a lentiviral vector expressing vascular endothelial growth factor delayed onset and slowed progression of amyotrophic lateral sclerosis in SOD1 transgenic mice even when treatment was only initiated at the onset of paralysis. This vector increased the life expectancy of these mice by 30% without toxic side-effects, making it one of the most effective treatments so far reported in an animal model. Intrathalcal administration of recombinant vascular endothelial growth factor in G93A SOD1 transgenic rats has also been reported to delay the onset of paralysis and prolong survival.

Stem-cell treatment

The potential restorative mechanisms of stem-cell treatment are still uncertain. In addition to replacement of lost cells, other processes including cell fusion, neurotrophic factor release, endogenous stem-cell proliferation, and transdifferentiation could be important. The feasibility and safety of implantation of autologous mesenchymal stem cells into the spinal cord has been tested in amyotrophic lateral sclerosis. No major adverse events arose, but there was no evidence of efficacy. The study was viewed largely as being premature and ethically questionable. Increases in donor-derived DNA have been reported after allogeneic haemopoietic stem-cell transplantation in amyotrophic lateral sclerosis, but the therapeutic potential remains uncertain. Much work remains to be done before stem-cell treatment can ever be regarded as even an experimental therapeutic modality in amyotrophic lateral sclerosis.

The way forward

Because of the shortage of satisfactory disease-modifying treatments, early diagnosis of amyotrophic lateral sclerosis has traditionally not been imperative. It will, however, be increasingly important for any attempts to develop more effective treatments. Encouragingly, findings of high-throughput technologies have shown potential proteomic and metabolic targets that might be used as disease-specific biomarkers. Such indicators could provide opportunities for early diagnosis and surrogate markers to monitor disease progression in clinical trials. A reliable method of showing subclinical upper motor neuron involvement would also be an important advance in clinical trial methodology.

Effective disease-modifying treatments for amyotrophic lateral sclerosis might include drug delivery via viral vectors or intrathecal administration. Viral vectors can also be used to accomplish gene transfer aimed at silencing a mutant gene, interfering with RNA, or replacing a defective gene. Such interventions are already underway in animal models. Future treatments might also entail multimodality regimens, as exemplified by approaches to antituberculous and cancer chemotherapy.

Since amyotrophic lateral sclerosis is likely to remain a progressive and fatal disease for several years, if not decades, further research into palliative care and symptomatic control will be of primary importance to improve quality of life of patients and their families. Although there has been substantial progress in our understanding of the disorder in the past 23 years, we are still some distance from fulfilling the aim of the Motor Neurone Disease Association to achieve a “World Free of ALS”. To quote Oscar Wilde, “the truth is rarely pure and never simple”, and we would also do well to remember the words of Winston Churchill: “This is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.”

Conflict of interest statement

JDM received speaker’s honoraria from several pharmaceutical companies, including Aventis, the manufacturer of riluzole, and Cephalon, the manufacturer of IGF-1, up until 2002. He was also an investigator in the dose-ranging trial of riluzole and in studies on IGF-1 (Cephalon), Xaliproden (Sanofi, and ONS 2006 (Onda)) but did not participate in data analysis or report preparation for any of these studies. He was chairman of the UK motor neuron disease interest group (funded by Aventis and Amgen) between 1998 and 2002. GDB was an investigator in three trials (European IGF-1 trial, riluzole open-label trial, and Xaliproden trial) and lead author of the European IGF-1 trial. He received the customary study fees for his centre and speaker’s fees from Cephalon, Rhone-Poulenc Rorer, and Sanofi.

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References