**MOTOR NEURONE DISEASE: (2) MANAGEMENT OF THE CONDITION**

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This second article on motor neurone disease focuses on disease management, including aspects of symptom control and disease modifying therapy, and provides an insight into the role of various multidisciplinary team members.

Motor neurone disease is a neurodegenerative condition that has devastating effects on both patients and their carers. Ideally, therefore, care should encompass the patient and extend to close family members. Emphasis should be on open and sensitive communication between all those involved and, at the same time, patients’ wishes should be respected. Information on motor neurone disease should be readily available for patients and carers and delivered in such a way as to take into account the cultural and psychosocial context of the patient and their family. With good communication between the patient and the various members of the multidisciplinary team involved in his or her care, all aspects of symptom control can be addressed. In order to avoid the stress and upheaval that can be caused by acute problems, it is important that decisions about a patient’s care are taken well in advance of any major changes in his or her condition. This should include planning for the future and liaising with the palliative care team in anticipation of the terminal phase of the disease.

**SYMPTOMATIC THERAPY**

Although advances have been made in the field of disease-specific treatments for motor neurone disease, the mainstay of treatment remains symptomatic management. Aspects of patient mobility, nutrition, respiratory difficulties and dysphagia control, including treatment of salivortha, are all important management areas to address. Communication, pain control, emotional support and other aspects of symptom management are also important.

All treatment plans should involve individualised alleviation of symptoms and complications. This ideally involves a multidisciplinary team approach to provide the medical, physical and psychosocial interventions necessary. This process is an ongoing one, as patient requirements will change as the disease progresses. Many symptomatic therapies have not yet been evaluated in rigorous therapeutic trials. However, published evidence for their use has recently been reviewed by the American Academy of Neurology and incorporated into its practice parameters document.¹

**MOBILITY**

Unfortunately, there are no pharmacological agents which will improve muscle weakness in motor neurone disease. Some neurologists will give a trial of anticholinesterase therapy, such as pyridostigmine, and although some patients may experience minor benefit initially, it is unlikely to be sustained.

In those patients with increased tone in the limbs, some improvement in mobility might be gained by using anti-spasticity agents. However, the benefits of these medicines may be outweighed by their potential side effects, which include an increase in muscular weakness resulting from reduction in muscle tone.

Non-pharmacological interventions are therefore important. Particularly important is assessment by a physiotherapy and occupational team, with input from the orthotics department, to ensure the provision of various aids and appliances. Ankle splints, wheelchairs, mobile arm supports and neck supports, plus various household appliances and modifications are some of the interventions available. These all help to alleviate symptoms that occur as a consequence of weakness and reduced limb function and they improve mobility and quality of life. Relevant physiotherapy can be taught to carers and patients to help prevent painful joint contractions. If financial help is needed for larger modifications around the home, help and advice regarding funding should be available from social services. Input from voluntary organisations, such as the Motor Neurone Disease Association, is often useful in the supply of various aids as well as being helpful in other aspects of patient care.

**CRAMPS AND FASCICULATION**

Fasciculations are often the first symptom of motor neurone disease. Cramps are also a common feature. Both can cause considerable discomfort. The drug of choice is quinine sulphate. Further treatment options are shown in Table 1.

**SPASTICITY**

In those patients with upper motor neurone features, spasticity can be a feature of the disease. If spasticity is mild, it may not cause any disability. However, if it is severe it can be a significant cause of disability. Treatment should be considered when alleviation of spasticity would improve physical function, alleviate pain, prevent complications, such as contractures and pressure sores, and ease nursing care.

Alleviation of spasticity should be approached using combined input from a physiotherapist, an orthotist and a physician. Initially, any unnecessary exacerbating factors, such as inappropriate seating or ill-fitting orthopaedic appliances, for example, should be dealt with. Physiotherapy, with passive movements and evaluation of correct positioning, is essential. The pharmacological treatment options are outlined in Table 1. The dosage of spasmylic agents should be titrated against the subjective clinical effect because it must be remembered that some degree of increased tone can often be useful to the patient. Increased

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**TABLE 1: SYMPTOMATIC TREATMENT FOR MOTOR NEURONE DISEASE**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramps and fasciculation</td>
<td>Quinine bisulphate 300mg at night. Carbamazepine initially 200mg daily. Phenytoin initially 100mg daily. Low dose diazepam. Baclofen initially as 5mg bd.</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Temporary benefit from anticholinesterase medications such as pyridostigmine.</td>
</tr>
<tr>
<td>Spasticity</td>
<td>Physiotherapy, Baclofen starting 5mg bd, increasing as needed, max 100mg Tizanidine initially 2mg daily, max 36mg Dantrolene initially 25mg daily, max 100mg Low dose diazepam</td>
</tr>
<tr>
<td>Urinary disturbance (rare)</td>
<td>Amitriptyline, oxybutinin</td>
</tr>
<tr>
<td>Pain</td>
<td>Address underlying cause. Combinations of non-steroidal anti-inflammatory drugs and non-narcotic agents initially. Opioids if the above measures fail</td>
</tr>
</tbody>
</table>

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tone can aid standing, for example, and flexor spasms can sometimes be used to facilitate dressing. If spasticity is severe, baclofen can be administered intrathecally via an implanted pump, though this is rarely necessary.

**Dysphagia management and nutritional care**

Motor neurone disease patients with bulbar symptoms are at risk of sub-optimal caloric and fluid intake with consequent worsening of muscle atrophy, weakness and fatigue. In addition, as the disease progresses, patients become increasingly at risk of aspiration pneumonia. Advice from a speech and language therapist regarding food types, consistencies, plus input from a dietician regarding the use of fluid thickeners and liquid nutritional supplements, may be sufficient initially to maintain adequate nutrition.

In the later stages of the disease, however, parenteral nutritional support using percutaneous endoscopic gastrostomy (PEG) might be required. Although the optimum timing of PEG insertion has not yet been fully determined, it should be considered in the setting of continuing weight loss (despite speech therapy and dietary advice), dehydration or aspiration with resultant chest infections. Other indications for PEG insertion include reaching the stage where oral intake of food becomes intolerable, especially if meals are ending prematurely because of dysphagia or if distressing choking episodes are regularly occurring.

The immediate benefits of PEG insertion are adequate nutritional intake, weight stabilisation and the provision of an alternative route for medication. The long-term benefits of PEG insertion remain unclear. Some studies have suggested that PEG insertion might prolong survival, on average, between one and four months, and the survival advantage appears to be greatest in patients with a vital capacity of greater than 50 per cent at the time of PEG insertion.

Patients can often continue to swallow some liquids and solids after PEG insertion, but the psychological stress that is often felt in trying to maintain caloric intake by mouth is greatly relieved. PEG insertion, however, is not without risk. The procedure usually involves some degree of sedation, and knowledge of a patient's respiratory capacity and the monitoring of oxygen saturation during and after the procedure are essential. For optimum safety it is suggested that intervention be carried out before the vital capacity reaches 50 per cent of that predicted. Potential complications of PEG insertion are: transient laryngeal spasm; localised infection at the abdominal site; gastric haemorrhage; failure to place PEG due to technical difficulties; death due to respiratory arrest; and peritonitis from leakage of gastric contents.

**Sialorrhoea**

There is no evidence that saliva production is increased in patients with motor neurone disease; rather the problem lies with poor saliva handling. But it is a symptom that can lead to significant social embarrassment for the patient. Management includes attempting to reduce saliva production and improve handling of secretions, or by techniques helping to divert and remove saliva. Besides advice regarding manually assisted coughing techniques to clear saliva, the key pharmacological therapy lies with anticholinergic medicines.

Oral atropine, which can be given in liquid as well as tablet form, is particularly useful. Starting at a small dose, such as 10mg daily, side effects such as salivation can be kept to a minimum. The dosage can then be built up, depending on symptom control and patient tolerability. Other potential side effects should be considered before prescribing, especially in the elderly, when its use may exacerbate other co-existing problems, such as the symptoms of prostatic hypertrophy or of constipation.

Hyoscine transdermal patches are also useful. A 1mg patch can be halved and positioned behind the ear, and then replaced behind the alternate ear every three days. If necessary, an increase to a full patch can be made. Atropine, again available in either liquid or tablet form, is an alternative choice of anticholinergic agent. The recommended daily dosage is of 300–600µg two to three times daily. This method needs to be explained to the patient to ensure they can be helpful and patients can be taught to use this themselves as and when required. If these methods do not alleviate the problem, low-dose irradiation to a single parotid gland can be considered, as can the use of botulinum toxin injections to the parotid gland to decrease saliva production.

Thick mucus can be an added problem. Carbocisteine, in tablet or liquid form, is a mucolytic which is often prescribed to facilitate expectoration by reducing sputum viscosity. It is useful in some patients and is usually given in a dose of 250mg three times a day initially, which can then be increased to 1.5g daily in divided doses if required. The alternative is a small dose of a beta-blocker, such as propranolol 10mg or metoprolol 50mg per day.

**Respiratory management**

Erect sitting and supine lung vital capacity (VC) measurements are useful in monitoring respiratory function. A decrease in a VC to 50 per cent of that predicted for the patient’s age and height is often associated with respiratory symptoms. A measurement of 25 to 30 per cent of predicted VC indicates a significant risk of impending respiratory failure or death. Therefore, in the setting of a falling VC measurement, regardless of symptoms, a number of planning steps should be taken.

Initial management includes the use of strategies that limit aspiration pneumonia, the reduction of oral secretions and positioning of the patient to best mechanical advantage. Physiotherapy advice regarding some breathing techniques is useful, as is the input from a respiratory medical team.

When significant respiratory muscle weakness is present, respiratory compromise often occurs initially during the night. Measurement of blood oxygen saturation during the night or, occasionally, full assessment in a sleep laboratory may be useful in evaluating nocturnal hypoventilation. In these patients the use of non-invasive intermittent positive pressure ventilation (NIPPV), via a nasal mask, may be helpful to control the symptoms associated with respiratory failure, including improvement in exercise tolerance, mobility, appetite, respiratory function and fatigue during the day. Patients with significant bulbar muscle weakness may have difficulty tolerating NIPPV and the use of more invasive methods of ventilatory support might need to be considered. However, full 24-hour intermittent positive pressure ventilation via tracheostomy is an option that seems to be chosen rarely by fully informed patients. The costs, in terms of both financial resources and support for the care giver, are substantial, and the implications of initiating such respiratory support must be clearly thought through and discussed with each patient.

An approach to the management of dyspnoea in the late and terminal phases of the disease is summarised in the Panel.

**Constipation**

Constipation can be a significant problem in motor neurone disease and can cause considerable discomfort. It can also exacerbate the problem of compromised respiratory function by pushing up the diaphragm. Management includes increasing dietary fluid and fibre intake. Bulk forming and osmotic laxatives and suppositories can be used and the dose adjusted as necessary. Medicines with constipating side effects may need to be adjusted.

**Emotional lability**

Pseudobulbar affect or pathological crying or laughing can be a troubling symptom. This emotional lability is not a mood disorder but an abnormal affective display that occurs in up to 50 per cent of patients. The tricyclic antidepressants imipramine and amitriptyline are useful agents, starting initially with a small dose of, say, 10mg (especially in the elderly), increasing as tolerated and as necessary.

Fluoxetine (20mg daily) and other selective serotonin reuptake inhibitors, such as citalopram (20mg daily), sertraline (50mg daily initially) and fluvoxamine (50–100mg daily initially), are also useful. Depression and anxiety are common symptoms, as are sleep disturbances. It must be remembered that there are multiple potential causes for these symptoms and any underlying problem needs to be identified and addressed. However, the use of antidepressant medication in these circumstances may be useful. Other potentially useful symptomatic treatments are covered in Table 1.
MANAGEMENT OF THE TERMINAL PHASE

Respiratory failure is the commonest cause of death in motor neurone disease and management to alleviate this potentially distressing symptom has already been discussed. Tremendous fear and anxiety surround the terminal stages of the disease and it is important to reassure both the patient and carers that any symptoms can be dealt with promptly as necessary. In most cases, the terminal stage and its potential problems will have been anticipated and prior planning can incorporate the palliative care team attached to a hospice.

DISEASE MODIFYING THERAPY

Anti-glutamate therapy — Riluzole

There is no therapy currently available which has a dramatic effect on slowing the progression of motor neurone disease. Riluzole (2-amino-6-trifluoromethoxybenzothiazole [Rilutek]), was the first drug to be licensed for the treatment of motor neurone disease in Europe and North America. Synthesised by researchers at Rhône Poulenc-Rorer (now Aventis Pharmaceuticals), it was launched in the UK in August 1996. One of the possible contributing factors to the motor neurone injury in the disease is an imbalance of the glutamate excitatory neurotransmitter system resulting in excessive action of glutamate on motor neurone receptors. Riluzole is a sodium channel blocker, able to cross the blood brain barrier, whose major action is inhibition of glutamate release.

The use of riluzole has largely been based on the results of two randomised, placebo-controlled trials, both incorporating patients with a diagnosis of definite or probable amyotrophic lateral sclerosis variant of the disease.20,21 The results of both trials showed a statistically significant, although modest, benefit in prolonging survival. Unfortunately, the trials did not include quality of life measures, though there is no evidence to suggest that riluzole prolongs the disease stage of severe disability.

Potential side effects include asthenia, somnolence, nausea and vomiting, vertigo, perioral parasthesia, dizziness and headache, all of which seem to be dose-related. Granulocytopenia has also been reported in a few patients and they should be warned to report febrile illnesses to their GP so a white cell count can be carried out. Riluzole is metabolised in the liver and dose-related increase in the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) can occur in up to 10% of patients. The level of increase in liver transaminases does not usually exceed three times the upper limit of normal, and if it does occur it usually does so in the first two months of treatment and will usually reverse spontaneously despite continuation of riluzole therapy. If the ALT rises three or more times above the normal limit, it is suggested that the liver function tests are monitored on a weekly basis. If the ALT rises five or more times above the normal limit, then the riluzole should be stopped. In view of the above, it is recommended that both full blood count and liver function should be monitored on a monthly basis for the first three months then every three months for the first year and at intervals thereafter.

Riluzole should not be given to patients with significant hepatic impairment or renal impairment. It is also contraindicated in pregnancy and breast feeding. No major interactions with other medicines have been documented.

Indications The use of riluzole has recently been reviewed by the National Institute for Clinical Excellence (NICE) and guidelines for its use have been published. The key recommendations for its use are that the diagnosis of motor neurone disease should be confirmed by a specialist physician with experience in the management of disease after appropriate investigations. It is currently only recommended for the treatment of the amyotrophic lateral sclerosis subtype of the disease in accordance with the current product license for riluzole.

This therefore excludes its use in those subgroups fitting into the possible and suspected categories, for example, progressive muscular atrophy and primary lateral sclerosis. Since it remains unknown whether these patients may benefit from riluzole, it is likely that it will probably still be the practice of many neurologists to prescribe riluzole in all subgroups until further trials are undertaken to address this particular issue, despite the NICE guidelines. The optimum time for starting neuroprotective therapy is uncertain, although it is logical to assume that it will have a greater effect if given as early as possible in the disease process when there is a greater population of surviving motor neurones.

Dosage and use The recommended daily dosage of riluzole is 100mg, as 50mg twice a day. The tablet can be crushed or suspended in liquid if the patient has difficulty swallowing and can be given down a PEG tube, although there is no information regarding the stability of tablets given in this way.

Riluzole is a relatively expensive medicine. A 28-day supply of tablets on the National Health Service is £286, which equates to £3,718 per patient per year. An additional cost, incurred for monitoring liver enzymes, has been estimated to be a maximum of £24 per patient, giving a total annual cost of treatment with riluzole of £3,742. It has been estimated that if riluzole were to be made available to all individuals with amyotrophic lateral sclerosis, the potential cost to the NHS would at maximum be around £7.5m. Given an estimated current level of funding, this represents an additional cost to the NHS of £5m. This does not take into account the additional NHS costs of patient survival. However, these costs must be weighed against the argument that these patients face a lethal disease for which no other therapy is available.

Other anti-glutamate therapies In 1998 a report was published showing a slowing of a clinical deterioration in motor neurone disease patients in a clinical trial of branched chain amino acids, which is postulated to modulate glutamergic transmission.22 However, this result was not confirmed in a large pan-European, multicentre, double-blind, placebo-controlled, randomised, parallel-group trial involving 760 patients (data unpublished).

Gabapentin is an anticonvulsant with anti-glutamate activity. It has been evaluated in motor neurone disease in a pilot therapeutic trial and showed a trend indicating potential slowing in the rate of decline of upper limb strength. This was not replicated in a further trial using higher doses of gabapentin. Lamotrigine, another anticonvulsant, has been unsuccessfully tried in motor neurone disease and a further anticonvulsant, topiramate, is currently under evaluation.

Neurotrophic factors Neurotrophic factors are peptides which are secreted by cells within the nervous system and are thought to contribute to the health and survival of motor neurones. They also have neuroprotective effects against stresses such as oxidative injury and glutamergic toxicity. Several neurotrophic factors, administered by subcutaneous injection, have been assessed in

An approach to management of dyspnoea

1. REVERSIBLE DYSPNOEA

1. Treat any underlying cause, eg, aspiration pneumonia with antibiotics

2. ACUTE ATTACKS OF INTERMITTENT DYSPNOEA

1. Short acting anxiolytic such as lorazepam 0.5–2mg sublingually
2. Inhaled opiates, eg, 5mg morphine nebulised
3. Diazepam enema 5mg
4. Midazolam slow intravenous injection 5–10mg, if very severe

3. CONSTANT DYSPNOEA IN TERMINAL PHASE

1. Initially opiates, eg, 5mg nebulised morphine, 2.5–5mg morphine orally four-hourly as required, 5–10mg subcutaneous diamorphine
2. Intravenous opiates if severe
3. Diazepam/midazolam especially for control of nocturnal distress
4. Chlorpromazine 25mg 4–12 hourly rectally or 12.5mg IV for terminal restlessness
5. Oxygen as needed
recent trials, so far with disappointing results. Ciliary neurotrophic factor (CNTF) showed no therapeutic benefit (and indeed had toxic effects at high doses). No definite positive therapeutic effect was observed with insulin growth-like factor (IGF-1) or brain-derived neurotrophic factor (BDNF). A trial of glial-derived neurotrophic factor administered by the intraventricular route was aborted. BDNF has recently been administered by continuous intrathecal catheter delivery via an implanted pump. Concerns have been expressed that these peptide neurotrophic factors may not reach motor neurones in adequate concentrations when administered by the subcutaneous route.

A multinational trial of the orally active agent, xaliproden (SR5746A), which appears to have neurotrophic-like effects on motor neurones, is also currently under analysis. Xaliproden has been evaluated as a single agent and in combination with riluzole therapy.

**Antioxidant therapy** There is growing evidence that oxidative stress plays a role in the pathogenesis of motor neurone disease. However, no large scale trials of antioxidant therapy have yet been conducted. An underpowered trial of N-acetylcysteine therapy showed a trend and antioxidant vitamin E delays disease onset, although the effect in humans is unproven, although many patients are empirically prescribed vitamin E and vitamin C because of the emerging evidence that free radicals may contribute to motor neurone injury.

**Future developments** Work involving cellular models of SOD1 related motor neurone disease has revealed agents showing a positive neuroprotective action. These include vitamin E, inhibition of caspases (proteolytic enzymes activated during apoptosis), SOD mimetic compounds, the antioxidant glutathione and copper chelators. In SOD1 transgenic mice there have also been a number of therapies which have been found to be neuroprotective. These include antioxidants, antiiapoptotic agents and compounds affecting mitochondrial function, such as creatine. These experimental models of motor neurone injury will be useful in the preclinical evaluation of new potential therapeutic agents.

In the next few years as we progress in our understanding of the disease pathogenesis in motor neurone disease, we are likely to see the development of further neuroprotective therapy which may well involve a “cocktail” of pharmacological agents aimed at different mechanisms contributing to the biochemical cascade of cell injury. In using such neuroprotective therapies to slow disease progression and prolong the life of the patient, careful attention must be paid to quality of life issues.

**References**