

Developments in the treatment of Motor Neurone Disease

Introduction

Motor neurone disease (MND) is a progressive neurodegenerative disorder affecting primarily lower motor neurones of the brainstem and spinal cord and upper motor neurones of the cerebral cortex. It is the third most common adult-onset neurodegenerative disease, with an incidence of 1-2 per 100,000. Approximately 5 to 10% of cases are familial. Affected individuals typically develop progressive muscle weakness and wasting that eventually involves both limb and bulbar muscles, combined with upper motor neurone signs such as brisk reflexes and a positive Babinski sign. The disease has a mean age of onset of 55 years. Death usually results from respiratory failure due to weakness of the respiratory muscles, an average of 3 years after onset of symptoms.

There are two aims in the treatment of motor neurone disease. The first, as this is an invariably fatal disorder, is the alleviation of symptoms to maintain quality of life. The second is to slow the progression of neuronal degeneration and ultimately to prevent further loss of motor neurones as early as possible in the course of the disease, before patients have developed significant disability. This article will describe the current symptomatic and disease modifying therapies available in MND, and discuss future directions.

NEUROPROTECTION

Pathogenesis of Motor Neurone Degeneration

An understanding of the molecular pathways that lead to motor neurone death is needed in order to target therapeutic strategies. Considerable advances have been made in the past few years through the development of cellular and animal models of motor neurone injury.

It is thought that multiple pathogenetic processes contribute to neuronal injury, to which motor neurones are selectively vulnerable. There is clinical and pathological evidence of the involvement of neurones outside the

motor system, however, and MND is now thought of as a multi-system degenerative disorder in which motor neurones are affected earliest and most severely¹. Features of motor neurones that underlie their vulnerability, and proposed mechanisms of injury are summarised in Figure 1.

A major advance in understanding motor neurone degeneration was the discovery in 1993 that one-fifth of familial cases are caused by mutations in superoxide dismutase 1 (SOD1), an antioxidant defence protein². Other genetic defects have been identified including genes coding for neurofilament proteins in some apparently sporadic cases of MND; a gene termed *alsin*, encoding a putative GTPase regulator in a rare juvenile form of MND^{3,4}, and in one family in *dynactin 1* which codes for a protein important in retrograde axonal transport.⁵ Other genetic loci linked to familial MND are being investigated in the hunt for disease causing mutations.

These findings may also shed light on the mechanisms of neuronal damage in sporadic MND, in which as yet unidentified genetic susceptibility and environmental factors are likely to interact to trigger the degenerative process via a number of pathogenic mechanisms:^{1,6-8}

- **Oxidative Stress:** An area of particular interest since the discovery of SOD1 mutations in familial MND, oxidative stress leads to accumulation of calcium and free radicals that trigger a cascade of damaging biochemical reactions.
- **Excitotoxicity:** Overstimulation of glutamate receptors causes excessive calcium influx and free radical production.
- **Neurofilament dysfunction:** Abnormal accumulation of neurofilaments, a characteristic feature of the pathology of MND, may be a primary process causing disruption in axonal structure and transport: motor neurone pathology is seen in transgenic mice that express abnormal neurofilament proteins. Alternatively neurofilaments may be prone to oxida-

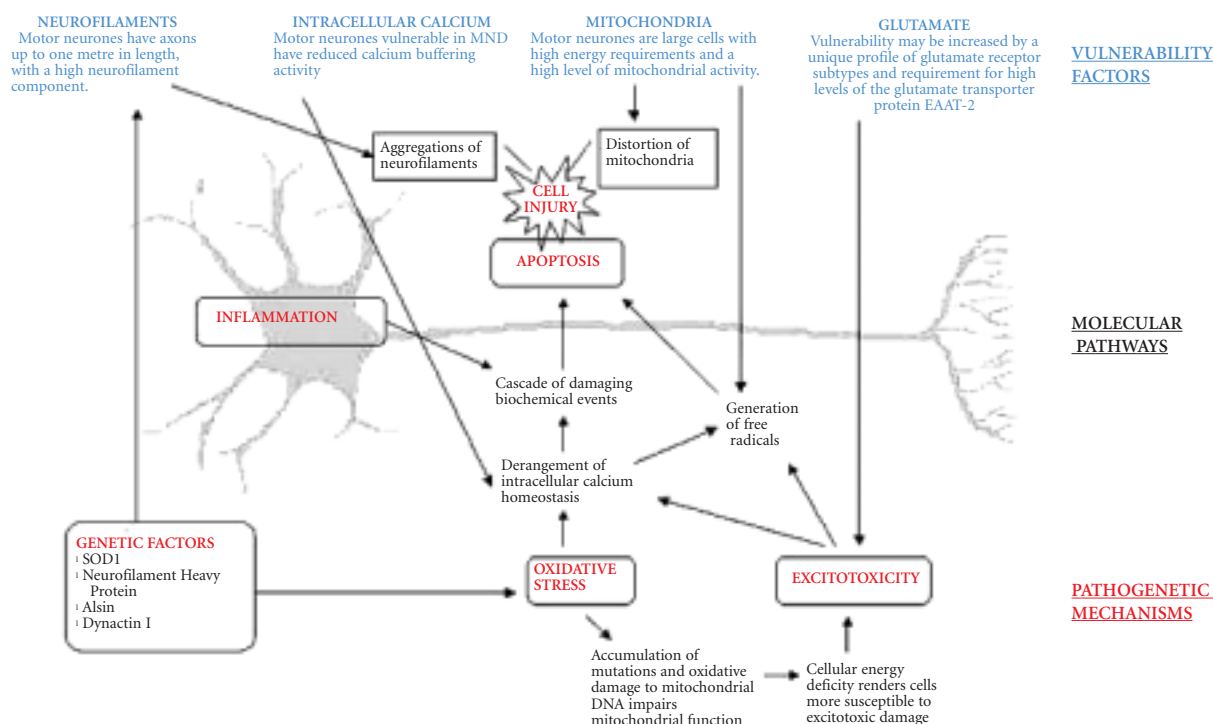


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Figure 1: Vulnerability factors and mechanisms of injury in MND^{1,7}



tive damage, as is seen in mice expressing mutant SOD1 protein.

- **Protein aggregation:** As in other neurodegenerative diseases, misfolding of proteins with the formation of intracellular aggregates is a feature of the pathology of MND, and is seen in the SOD1 transgenic mouse model due to misfolding of mutant SOD1. It is not known whether such aggregated proteins play a role in pathogenesis, or are harmless bystanders.
- **Mitochondrial dysfunction:** Mitochondria show early disruption in mouse models of MND, and are particularly susceptible to oxidative and free radical damage.
- **Inflammation:** Reactive microglia and astrocytes are abundant in pathologically affected areas in human MND. These may release pro-inflammatory molecules that propagate the neurodegenerative process.
- **Apoptosis:** There is evidence that the final common pathway of these processes is activation of the apoptotic cell death pathway which leads to death of motor neurones.

Neuroprotective Therapies

These insights into the mechanisms of neuronal degeneration have led to the development of a number of compounds which protect neurones in cell culture and in animal models of MND. Over 50 potential neuroprotective agents have been tested in clinical trials which have been extensively reviewed elsewhere.^{9,10} The larger trials, and their theoretical and experimental basis are summarised in Table 1.

Riluzole

One of these, riluzole (Rilutek) has been shown to slow significantly disease progression in humans. It is the only neuroprotective agent licensed for use in MND. It is a sodium channel blocker whose primary mechanism of action is to reduce excitotoxicity through inhibition of glutamate release although it has been shown to have several other potentially neuroprotective effects.¹⁰

Two double-blind placebo-controlled trials of riluzole have been carried out in more than 1100 patients.¹¹⁻¹³ A Cochrane review of riluzole therapy in MND¹⁴ concluded that there is a statistically significant, although modest, effect in prolonging survival by approximately 2-3 months. A modest improvement in limb and bulbar function was seen, but no clear effect on muscle strength was demonstrated, and neither trial evaluated quality of life.

In view of the high cost to benefit ratio, there has been

controversy about the use of riluzole worldwide. In the UK, its use is recommended by the National Institute for Clinical Excellence (NICE) which estimated the cost of therapy to be £34000 to £43500 per quality-adjusted life year (QALY)¹⁵. The NICE guidelines and other characteristics of riluzole are summarised in Table 2.

Other Neuroprotective Agents

As shown in Table 1, several compounds that appeared to protect neurones from degeneration in cell culture and animal models have had disappointing results in clinical trials. There are two possible explanations for this. Firstly, the models used may not accurately reproduce human disease. Secondly problems with the design and methodology of clinical trials in the past (Information Box, page 18) could mask a modest clinical benefit.

To improve the design and implementation of clinical trials in MND, the World Federation of Neurology published consensus guidelines in 1998.¹⁶ These recommended the use of El Escorial/Airlie diagnostic criteria¹⁷, defined common inclusion and exclusion criteria and endpoints, including quality of life, and advised on techniques for measuring disease progression.

Future Directions

1. **Novel Disease Modifying Therapies:** Several potential neuroprotective compounds are currently undergoing clinical trials (see Table 3, page 17).
2. **Drug Cocktails:** By analogy with other previously incurable diseases, such as the haematological malignancies and HIV/AIDS, it is likely that neuroprotective therapies developed in the future will be combined with riluzole in a drug 'cocktail' to affect the pathway of neuronal degeneration at multiple levels.
3. **High throughput drug development:** Automated laboratory assays of neurodegeneration can rapidly screen thousands of chemicals to identify lead compounds for drug development. The traditional reluctance of pharmaceutical companies to invest heavily in rarer diseases such as MND has recently been addressed by the emergence of non-profit-making biotech companies using high-throughput drug screening to identify compounds of interest.¹⁸
4. **Stem Cell Research:** The ultimate goal of MND research is not only to halt neuronal degeneration, but then to restore the original structure and function of the motor nervous system. Pluripotent stem cells, capable of differentiating into different cell types are



Figure 2: A PEG Tube (24 hours post insertion) in a patient with MND



Figure 3: The use of NIPPV in a patient with MND

the obvious candidate for this function. However stem cell technology is at an early stage and large scale clinical trials are likely to be a long way off.¹⁹

SYMPTOMATIC TREATMENTS

Although neuroprotective therapy in MND is still very limited, symptomatic treatment can substantially alleviate distress and improve quality of life.

There is a growing tendency in the UK for patients with MND to be managed in specialist clinics. This allows for the coordination of a multi-disciplinary team with experience of MND, which includes nursing staff with specialist training, physiotherapist, occupational therapist, speech therapist, dietician, social worker and orthotist. Considerable support is also provided by patient associations such as the MND association (www.alsmndalliance.org)

The management of common symptoms in MND is summarised in Table 4. Respiratory symptoms, nutritional support and terminal care are discussed in more detail:

Respiratory Symptoms

Respiratory muscle weakness develops insidiously during the course of ALS, causing dyspnoea, orthopnoea and

symptoms of carbon dioxide retention, which include daytime somnolence, morning headaches and lack of restorative sleep with frequent waking.

The management of respiratory complications includes early recognition and treatment of aspiration pneumonia with antibiotics; chest physiotherapy and postural drainage to clear secretions; sleeping in an upright position to allow patients to breathe more easily at night; sublingual lorazepam for severe anxiety and dyspnoea and small doses of opiates to ease breathlessness in terminal stages.⁶

Non-invasive positive pressure ventilation (NIV) used overnight has been shown to alleviate symptoms of chronic hypoventilation, to improve significantly several measures of quality of life²⁰, and in two small studies also prolonged survival^{21,22} (Figure 2). In the UK few patients are treated with NIV (2.6-3.5% of all MND patients), and there is marked variation in clinical practice.²³ This may partly be due to regional variation in the availability of NIV. The early signs and symptoms of hypoventilation are also subtle and easily overlooked, and there is no clear consensus on the optimal criteria for initiation of NIV, or the best method of assessment to detect impending respiratory failure.²⁴ The results of a

Table 1: RECENT CLINICAL TRIALS IN MND

Pathogenetic Mechanism	Therapeutic Candidate	Rationale	Result of Clinical Trial in MND Patients
Excitotoxicity	Riluzole	Anti-convulsant that blocks presynaptic glutamate release. Slowed disease progression in SOD1 mouse model of MND ²⁹	Modest significant survival benefit ^{11,12,13}
	Branched Chain Amino Acids	Activate glutamate dehydrogenase to reduce glutamate levels	Recent Cochrane review concluded no significant benefit. ³⁰
	Gabapentin	Reduces glutamate activity. Slowed disease progression in SOD1 mutant mouse models of MND. ²⁹	Trend towards slowing of disease progression in pilot trial ³¹ not duplicated in further trial. ³²
	Topiramate	Reduces glutamate activity. Protects against motor neurone degeneration <i>in vitro</i> . ³³	No significant benefit. ³⁴
Oxidative Stress	Vitamin E (✓ -tocopherol)	Supplementation of the diet of SOD1 transgenic mice with vitamin E delayed onset of symptoms and slowed disease progression. ²⁹	No survival benefit. Significantly more patients remained in a milder disease state after 12 months treatment. ³⁵
	N-acetylcysteine	N-acetylcysteine is a precursor of the antioxidant glutathione	No significant difference in survival or disease progression in an under-powered trial. ³⁶
Neurotrophic Effects	CNTF (subcutaneous)	These neurotrophic factors promote survival of motor neurones <i>in vitro</i> and arrest disease progression in the <i>wobbler</i> mouse model of MND ³⁷	No benefit shown, detrimental effect at higher doses. ^{38,39}
	BDNF (subcutaneous and intrathecal)		No significant benefit ⁴⁰ Intrathecal trial terminated early due to increased incidence of adverse events in the treated group (unpublished)
	IGF-1 (subcutaneous)	Promotes motor neurone survival in several models of neuronal injury ^{41,42}	Significant slowing of disease progression in US trial not duplicated in a European study. Cochrane review concluded IGF-1 use could not be recommended. ⁴³
Mitochondrial Dysfunction	Creatine	Phosphocreatine allows the rephosphorylation of ADP to ATP. Oral creatine supplementation may improve cellular energy deficits ⁴⁴ , and prolongs survival in SOD1 transgenic mice.	No significant benefit ⁴⁵

Abbreviations: CNTF ciliary neurotrophic factor, BDNF brain derived neurotrophic factor, IGF-1 Insulin like growth factor - 1

controlled trial of NIV versus supportive care being undertaken in the UK are currently awaited.

Mechanical ventilation via tracheostomy can theoretically extend a patient's life indefinitely but poses considerable ethical dilemmas, and is rarely practiced in the UK, or requested by fully informed patients.

Nutritional Support

Weight loss is universal in MND patients, due to dysphagia and loss of muscle mass. Weight loss, malnutrition and dehydration can aggravate muscle weakness and shorten lifespan, whilst frequent choking spells can make mealtimes intolerable. In early dysphagia, nutrition may be maintained by nutritional supplements, or by altering food consistency. Recipe books are available from the MNDA to help with this.

However, if these measures do not prevent continuing weight loss or dehydration, or if mealtimes are ended prematurely due to choking or dysphagia, enteral feeding should be considered. Percutaneous endoscopic gastrostomy (PEG) feeding in MND has been the subject of a recent Cochrane review²⁵, and represents one of the major advances in symptomatic care for patients, leading to weight stabilisation and adequate nutritional and fluid intake, although a survival benefit

has not been convincingly shown. The need for PEG feeding should be anticipated as the risks of the procedure are higher once a patient's FVC falls below 50%.²⁴

In some patients, technical difficulties may be experienced in the insertion of a PEG tube. In this situation, a radiologically guided method may be used²⁶. In patients with a low vital capacity, the use of NIV during PEG inserion has been shown to improve tolerance and safety of the procedure.^{27,28}

Terminal Care

If MND patients are not ventilated, they will almost always die in their sleep from hypercapnic coma. In the terminal phases of illness the aim of treatment is to ensure that the patient is comfortable, and opiate and anxiolytic medication should be used as required to alleviate discomfort or distress.

Table 2: RILUZOLE THERAPY IN MND

<u>NICE Guidelines</u>	<ul style="list-style-type: none"> ● Riluzole is recommended for the ALS form of MND ● Therapy should be initiated by a neurologist, with routine supervision through locally agreed shared care protocols.
Dosage	50mg twice daily
Side Effects	Nausea and vomiting Asthenia, somnolence Headache, dizziness, vertigo
Serious Adverse Effects	<ul style="list-style-type: none"> ● Elevation in liver transaminases Regular monitoring of liver function is advised (every month for 3 months, every 3 months for a further nine months then annually thereafter) ● Rare cases of neutropaenia have been reported White cell count must be checked in the case of febrile illness
Contraindications	Renal and hepatic impairment Pregnancy and breast-feeding

Table 3: NEW POTENTIAL NEUROPROTECTIVE AGENTS BEING EVALUATED IN MND¹⁰

Compound	Mechanism	Evidence
Xaliproden	Oral neurotrophic agent	Neurotrophic effects in animal models of neurodegeneration
Minocycline	Inhibits activation of caspases in the apoptosis cascade and microglial activation.	Prolonged survival in SOD1 transgenic mouse model of MND
Celecoxib	A free radical scavenger and inhibitor of cyclooxygenase (COX). Marked increases in COX-2 have been found in MND spinal cord	
Co-enzyme Q10	A cofactor in the mitochondrial respiratory chain and endogenous anti-oxidant ⁴⁸	
Ono-2506	An astrocyte modulator	Neuroprotective effects in cell culture and animal models of neuronal injury.
Pentoxifylline	A phosphodiesterase inhibitor already used in the treatment of peripheral vascular disease	Identified as a potential therapeutic target for ALS through screening in transgenic mice
Novartis TCH346	Anti-apoptotic agent currently undergoing clinical trial in MND.	

Information Box: DIFFICULTIES IN MND CLINICAL TRIAL DESIGN

1. Many trials are underpowered to detect a modest clinical benefit. Approximately half the trials carried out since 1990 have involved 18 patients or less for a mean duration of 24 weeks.⁹
2. MND is a heterogeneous disorder, with features that cause inherent difficulties in trial design:¹⁰
 - **Endpoints difficult to define:** Survival can be extended by respiratory support and PEG feeding.
 - **Disease progression hard to measure reliably:** Certain parameters such as muscle strength and bulbar function are difficult to measure reliably. Use of various measures of disease progression has made comparison of past trials difficult.
 - **Diagnostic variability:** Diagnosis is clinical and can be difficult. It is made at an ill-defined point in the course of the disease when an estimated 80% of motor neurones have already been lost⁴⁶, and it is not possible to detect a pre-clinical phase. Trials cover only a small proportion of the disease course, reducing chances of detecting any neuroprotective effect.
3. Difficulty in translating the effects of drugs beneficial in mouse models, such as mutant SOD1 transgenic mice into effective human neuroprotective therapies: Several drugs effective in SOD1 transgenic mice have not been shown to be beneficial in human trials, for example gabapentin^{31,32} creatine⁴⁵ and vitamin E³⁵. Several reasons have been put forward for this, including starting therapy presymptomatically in mice, and deficiencies in the design of mouse trials including failure to take into account gender and litter effects.⁴⁷

Table 4: SYMPTOMATIC THERAPY IN MND ^{24,49}

SYMPTOM	TREATMENT
Muscle weakness and Fatigue	<ul style="list-style-type: none"> • Physiotherapy to prevent muscle contractures and joint stiffness • Devices to maintain mobility and independence such as ankle-foot orthoses, head supports, mobile arm supports, bathroom aids etc • Acetylcholinesterase inhibitors (pyridostigmine) can cause a short term improvement in fatigue in some patients
Fasciculations Painful muscle cramps are common Spasticity causes pain and decreased mobility	<ul style="list-style-type: none"> • Anti-spasticity agents (Baclofen, Tizanidine): Dose must be carefully titrated as loss of tone can worsen mobility • Quinine sulphate for cramps • Low-dose diazepam for cramps or fasciculations
Sialorrhoea (drooling) due to impaired swallowing and facial muscle weakness causes sore lips, dehydration, and embarrassment	<ul style="list-style-type: none"> • Hyoscine transdermal patches, amitriptyline or atropine • Portable suction devices. • Low dose parotid irradiation may be considered if drug treatment is not successful. • B-blockers or carbocysteine reduce viscosity of secretions.
Pseudobulbar Affect : Inappropriate laughter or crying that often accompanies corticobulbar involvement	Responds well to amitriptyline or selective serotonin reuptake inhibitors (SSRIs)
Psychological Problems: Depression and Anxiety	A grief reaction is a normal response to a devastating diagnosis. Clinical depression is also common and underdiagnosed. It can be treated with tricyclic antidepressants or SSRIs.
Sleep Disorders	Treatment should be directed at the cause of insomnia. Common causes in MND are respiratory insufficiency, anxiety, depression, muscle cramps, and inability to change position. Use of sedatives should be avoided unless other options fail.
Constipation is common secondary to immobility, dehydration and weakness of abdominal muscles	<ul style="list-style-type: none"> • Review medications (Analgesics and anticholinergics worsen constipation) and ensure adequate fluid intake • Bulk-forming or osmotic laxatives, glycerol suppositories
Musculoskeletal Pain is common due to abnormal stresses on bones and joints	Non-steroidal anti-inflammatories and physiotherapy are most effective
Dysarthria	Simple strategies to improve communication can be taught by a speech therapist. When these become ineffective, a variety of communication aids are available, such as a light-writer
Dysphagia	See text
Dyspnoea	See text
Terminal care	See text

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