Motor neuron disease: systematic reviews of treatment for ALS and SMA

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Introduction: There is no curative treatment for the common motor neuron diseases, amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy. Nevertheless, there is an increasing volume of published studies. This review assesses the current evidence for treatment of these conditions.

Sources of data: Primarily, the systematic reviews of the Cochrane Collaboration, with additional reference to other systematic reviews and online sites.

Areas of agreement: Riluzole remains the only medication with demonstrated efficacy and regulatory approval for the treatment of ALS.

Areas of controversy, growing points and areas timely for developing research: The design of clinical trials and the publication of unsatisfactory studies, in both human and animal models, continue to cause confusion in advising on patient management. Improvements in trial design, critical assessment of studies for publication and avoidance of bias towards publication of positive results are needed. A better understanding of pathogenesis should lead to more potent interventions.

Keywords: motor neuron disease/amyotrophic lateral sclerosis/spinal muscular atrophy/treatment/therapy/systematic review/Cochrane Collaboration

Introduction

Amyotrophic lateral sclerosis (ALS), or motor neuron disease (MND), remains one of the most devastating, and incurable, neurological diseases. For the purpose of this review, ALS and MND are considered to be synonymous (ALS/MND). Although appearing to be relatively rare, as most individuals survive from diagnosis to death by only 2 or 3 years, the incidence is around 2–3 per 100 000, and around 1 in 500 individuals will die of the condition. The underlying causes remain uncertain, but appear to be multifactorial, including genetic and environmental causes.1 Riluzole is licensed for the slowing of progression of disease, but with
relatively mild effect. There are also symptomatic treatments. In the absence of any curative treatment, and a limited understanding of the causes of the disease, a wide number of potential treatments have been considered. A few of these have been subjected to clinical trials (Table 1). The methodology of the clinical trials has not always been adequate. Neurologists, patients and others involved in the management of patients with ALS/MND may seek up-to-date advice on potential treatments. There has been a relatively recent expansion in the availability of systematic reviews of therapeutic interventions for ALS/MND, and it is timely to review the availability and findings of these reviews.

Many of these reviews are published as part of the Cochrane Collaboration, but may not be readily available in all countries. Some of these are however available in standard journal articles.

The key feature of a systematic review is that the methods are explicit. The literature search should be thorough and rigorous. Valid studies may be combined using techniques such as meta-analysis. The methodology will include a grading of the quality of the studies. There will also be an attempt to access results of studies which have not been published, often due to a negative result. The aim is to provide an objective appraisal of the evidence available and to remove the bias inherent in most forms of review. Systematic reviews provide the foundation for evidence-based medicine. The results should be accessible to a wide audience including neurologists, other health-care professionals, patients and carers.

The Cochrane Collaboration is an international not-for-profit and independent organization, dedicated to making up-to-date, accurate information about the effects of healthcare readily available worldwide. It was founded in 1993 and is named after Archie Cochrane, a British

### Table 1: Potential treatments for MNDs considered in this review.

- **Glutamate blocking agents**—riluzole
- **Antioxidants**—vitamin C, vitamin E, L-methionine, selenium, acetylcysteine, selegiline, dehydroepiandrosterone
- **Ciliary neurotrophic factor (CNTF)**
- **Insulin-like growth factor (IGF-I)**
- **Creatine**
- **Phenylbutyrate**
- **Gabapentin**
- **Thyrotopin-releasing hormone**
- **Branched chain amino acids**
- **Lithium**
- **Minocycline**
- **Therapeutic exercise**
- **Enteral tube feeding**
- **Non-invasive ventilation**
- **Treatment of sialorrhea**—amitriptyline, hyoscine, botulinum toxin, radiotherapy

Riluzole is the only medication demonstrated to be effective in prolonging survival in ALS/MND. Enteral feeding and non-invasive ventilation also appear effective.
epidemiologist (www.cochrane.org). The Cochrane Library currently contains 3737 complete reviews and 1939 protocols. The review is structured to have background, objectives, methods of the review, results and discussion. The methodology of the review is peer reviewed, the review is conducted by at least two individuals, and is peer reviewed before publication. The primary form of publication is in the Cochrane Library. This is an electronic library, available on CD (currently five discs) or on the Internet. This allows regular updating of reviews. The results should be accessible to a wide audience including neurologists, other health-care professionals, patients and carers.

There are currently 11 reviews for ALS/MND and 7 protocols awaiting completion of the review. There are a further 11 reviews for spinal muscular atrophy (SMA), another disease of motor neurons. There are also reviews for more generic neuromuscular and neurological problems.

Cochrane reviews of treatment for ALS

Glutamate blocking agents

Riluzole is currently the only medication approved by regulatory authorities for the treatment of ALS, including Europe, the USA, and Australia. The first studies were based on the hypothesis that glutamate excitotoxicity contributes to the neuronal death in ALS/MND, with riluzole being a glutamate release inhibitor. Miller et al.\(^2\) identified four randomized controlled trials, in a total of 974 riluzole-treated and 503 placebo-treated patients.\(^3\)–\(^6\) They chose the pooled hazard ratio based on per cent mortality (or tracheostomy) for 100 mg riluzole versus placebo over all time points. The statistical analysis of the trials is complex. For the first two trials, the hazard ratio was 0.80 (95% confidence interval 0.64–0.99, \(P = 0.042\)). But when a third trial (of older and more seriously ill patients) was included, the overall treatment effect estimate fell just short of significance (\(P = 0.056\), hazard ratio 0.84; 95% confidence interval 0.70–1.01) (Fig. 1). There was a 9% gain in the probability of surviving 1 year (from 57% on placebo to 66% on riluzole). There was a small positive effect on bulbar and limb function, but not on muscle strength. When the data for the 100 mg dose for the three trials were pooled, the median survival was 14.8 months for riluzole and 11.8 months for placebo, a difference of 3 months (Fig. 2). Miller et al.\(^2\) conclude that riluzole 100 mg daily is reasonably safe and probably prolongs median survival by about 2–3 months in patients with ALS/MND. It would be interesting to have further studies of riluzole, in defined groups of patients, for a longer
duration, but this is unlikely given the small effect and the search for more effective medication.

**Antioxidant treatment**

Antioxidants have been considered and used for many years as potential treatment of ALS/MND. Many patients still take antioxidants such
as vitamin C and vitamin E. Vitamin E at high doses (>1000 mg daily) may increase the risk of haemorrhagic stroke and premature death. Orrell et al.\textsuperscript{7} identified nine randomized controlled trials. There was insufficient evidence to confirm efficacy of vitamin E 500 mg bd,\textsuperscript{8} vitamin E 1 g five times daily,\textsuperscript{9} a combination of L-methionine, vitamin E and selenium (Alsemet),\textsuperscript{10} or acetylcysteine 50 mg/kg daily subcutaneously.\textsuperscript{11} Other antioxidants considered, but with insufficient evidence, include selegiline and dehydroepiandrosterone. A small-molecule antioxidant AEOL-10150 has been under development. Vitamin C and vitamin E are low cost vitamins, usually well tolerated, and continue to be used by some physicians and patients, and there is no clear contraindication, despite lack of proven efficacy.

**Ciliary neurotrophic growth factor**

Ciliary neurotrophic growth factor (CNTF) is a neurotrophic factor, which was shown to promote motor neuron survival in cell cultures and rodents, including a slowing of disease progression and improvement of muscle strength in the wobbler mouse model of ALS/MND. Bongioanni et al.\textsuperscript{12} identified two randomized controlled trials, with a total of 1300 patients with ALS/MND. Recombinant CNTF was injected subcutaneously three times a week in the first trial\textsuperscript{13} and daily at a lower dose in the second.\textsuperscript{14} No significant efficacy was demonstrated, and at higher doses, side effects were observed.

**Insulin-like growth factor**

Insulin-like growth factor I (IGF-I) is a naturally occurring peptide with neurotrophic effects. Beneficial changes have been reported in a number of ALS/MND and other neuropathy models, including G93A SOD1 transgenic mice. Mitchell et al.\textsuperscript{15} identified two randomized controlled trials suitable for inclusion. Using subcutaneous recombinant human IGF-I (rhIGF-I) daily, in a European trial with 124 receiving rhIGF-I 0.1 mg/kg/day and 59 placebo, no significant change in the Appel ALS Rating Scale (AALSRS) score was found at 9 months treatment.\textsuperscript{16} In a North American trial with 89 receiving rhIGF-I 0.05 mg/kg/day, 87 receiving 0.1 mg/kg/day and 90 placebo, there was a significant benefit on change in AALSRS score at 9 months.\textsuperscript{17} The combined analysis of both trials showed a significant benefit on change in AALSRS score in the treated group (Fig. 3). Mitchell et al.\textsuperscript{15} concluded that the available trials do not allow a definitive assessment of the clinical efficacy of rhIGF-I in ALS/MND. Mitchell et al. had concerns including small sample sizes, short study duration and...
A third randomized controlled trial from the USA has recently been published (and not yet included in the Cochrane review). Patients with ALS received 0.05 mg/kg rhIGF-I subcutaneously twice daily, or placebo, for 2 years. There was no benefit on change in manual muscle score, survival or rate of change of ALSFRSR. Variants of IGF-I are also recognized, with potential benefits including altered specificity and the possibility of improved modes of administration.

**Therapeutic exercise**

A common question of physicians and patients is the effect of exercise on ALS/MND. There are theoretical reasons to suggest that excess exercise may be deleterious to compromised motor nerves and muscle, but equally there are the normal benefits of exercise on nerve and muscle growth and sustainability. Three studies in SOD1 mice demonstrated a slowing of disease progression with moderate intensity endurance exercise. A fourth study found a detrimental effect of high endurance exercise training in male mice only. Dal Bello-Haas et al. identified two randomized controlled trials, a moderated load endurance exercise in 25 people with ALS/MND, and a thrice weekly moderate load and moderate intensity resistance exercise in 27 people. Combining the two studies, after 3 months, there was a significant improvement in the ALSFRS score in the exercise compared with the control group (Fig. 4). Dal Bello-Haas et al. concluded that the studies were too small to determine whether exercise for people with ALS/MND is beneficial or harmful.

**Enteral tube feeding**

Enteral tube feeding is commonly used in ALS/MND to maintain adequate nutrition and hydration. This is most commonly performed...
using percutaneous endoscopic gastrostomy (PEG), and also radio-
logically inserted gastrostomy (RIG). Langmore et al.23 did not ident-
ify any randomized controlled clinical trials in ALS/MND. They
identified 10 controlled trials and 1 comparing PEG and RIG.
Fifty-four uncontrolled trials were considered appropriate for con-
sideration. The benefit of enteral nutrition is generally thought to
have been demonstrated, and it would be difficult to perform a ran-
domized controlled trial without enteral nutrition. Overall, in the
(non-randomized controlled) trials considered, there was a positive
benefit of PEG on survival, both in bulbar and limb onset patients.
Nutrition was also improved. Langmore et al.23 also concluded that
lower vital capacity at the time of PEG has not been shown to be
associated with poorer outcome when non-invasive positive pressure
ventilation (NIPPV) is used or when RIG is substituted.

Drug therapy for pain

Pain is a common problem in ALS/MND, especially in the later stages.
Much of this relates to neuromuscular weakness, including the effects
of posture and immobility. Severe pain has been reported in up to 20%
of patients with ALS/MND. Brettschneider et al.24 did not identify any
randomized controlled trials of drug therapy for pain in ALS.
Management remains common to other conditions including non-
steroidal anti-inflammatory drugs and opioids. Cannabis was noted to
be used much less frequently in ALS/MND than in other diseases such
as multiple sclerosis, AIDS or cancer.

Treatment of spasticity

Spasticity is a common feature of ALS/MND, and for some patients it is
severe, both in general disability and in pain. Ashworth et al.25 searched
for randomized controlled trials of many potential modalities of

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Fig. 4 A meta-analysis of change in ALSFRS score, comparing therapeutic exercise against
normal activity, of ALS/MND patients for 3 months, for two studies described in the text. A
benefit of exercise is demonstrated. Dal Bello-Haas et al.,20 copyright Cochrane
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spasticity therapy in ALS/MND—physical therapy, prescription medicines, non-prescription medications, chemical neurolysis, surgical interventions and alternative therapies. They identified only one randomized controlled trial which met their criteria. This was a study of moderate intensity endurance activity in 25 patients with ALS/MND.\textsuperscript{21} At 3 months, patients performing 15 minute exercises twice daily had significantly less spasticity overall, compared with usual activities. Ashworth \textit{et al.}\textsuperscript{25} concluded that the single trial was too small to determine whether the exercise was beneficial or harmful. They comment that research is needed to test whether anti-spasticity medication such as baclofen or dantrolene is beneficial or causes harm by worsening muscle weakness and function. Clinical experience suggests that baclofen, dantrolene and similar medications for spasticity have a place in the management of patients with ALS/MND, but the dose needs careful adjustment, related to the progressive nature of the disease. It is probably difficult to design an appropriate randomized controlled trial in this situation.

\textit{Familial MND}

Several genes are linked to classical ALS, in particular SOD1 (copper/zinc superoxide dismutase), TARDBP (TAR DNA-binding protein 43) and FUS (fused in sarcoma/translated in liposarcoma),\textsuperscript{26} together with genes linked to other motor neuron disorders. There is the consideration whether, for example, ALS/MND associated with SOD1 mutations is a specific disorder, which may respond to specific treatment. Benatar \textit{et al.}\textsuperscript{27} attempted to determine whether subgroups of familial ALS patients could be isolated from randomized controlled trials of ALS/MND (sporadic and familial combined). They obtained data from only four large studies, including 41 familial ALS/MND patients. Data could not be obtained from 25 potentially eligible studies. In clinical practice, it is assumed that all ALS/MND patients will respond similarly to potential treatment, but it is important that in future, patients with specific genetic mutations are identified and analysed as subgroups. It may be that some gene-directed therapies will be targeted on specific genetic conditions.

\textit{Cochrane reviews of treatment for SMA}

A number of Cochrane reviews are available for SMA. Generally, this refers to the genetically defined, or diagnosed condition, related to changes in the SMN gene. Most of these individuals are children, but a number of adults may present with SMA, especially type IV (proximal, adult form), with age of onset after 35 years.
SMA type I (Werdnig–Hoffman) affects children from birth, they are never able to sit, and usually die by age 2. Bosboom et al.28 identified one randomized controlled trial, which compared riluzole with placebo.29 Three children treated with riluzole were still alive at age 30, 48 and 64 months, whereas all patients died in the placebo group. Only 10 patients were included in the study, which was not fully enrolled due to funding problems. Bosboom et al.28 concluded that no drug treatment has been shown to have a significant efficacy in SMA type I, but a larger trial of riluzole is needed.

In a separate review, Bosboom et al.30 identified four randomized controlled trials for SMA type II and III. Children with SMA type II (late infantile) never walk without support, survive beyond 2 years of age and may live to adolescence or longer. Children with SMA III (Kugelberg–Welander) develop symptoms after the age of 18 months, walk at some time and life expectancy is normal. Trials of creatine,31 phenylbutyrate,32 gabapentin33 and thyrotropin-releasing hormone34 did not show significant benefit or adverse effects.

Other systematic reviews of treatment for ALS

Not all published studies of therapy in ALS/MND have yet been included in Cochrane reviews. Some of these are in protocol form (published in the library) and others not yet addressed. None of these pharmaceutical agents have been demonstrated to be clinically effective. Worthy of note is a systematic assessment of neuroprotective agents to be considered for clinical trials in ALS/MND.35 At that time, 20 drugs were considered suitable for further investigation in patients with ALS/MND. Talampanel and tamoxifen had completed early phase II trials. Ceftriaxone, minocycline, ONO-2506 and IGF-I were in phase II trials in ALS/MND. Other agents considered appropriate for further study included AEOL-10150, arimoclomol, celastrol, coenzyme Q10, copaxone, IGF-1 viral delivery, memantine, NAALADase inhibitors, nimesulide, scriptaid, sodium phenylbutyrate, thalidomide and trehalose.

A systematic review of botulinum toxin or radiotherapy for sialorhoea in ALS was performed by Stone and O’Leary.36 Problems with saliva clearing or swallowing are common in patients with ALS/MND. A range of medications may be used, in particular anticholinergics including hyoscine and amitriptyline. In more serious cases, botulinum toxin or radiotherapy may be considered. They identified five studies, with 28 patients, of botulinum toxin injection, with benefit in some patients with intraglandular injection, but some problems with retrograde injection into the salivary ducts. Two studies, with 27 patients of
radiotherapy, showed benefit. The small numbers and quality of the studies made it difficult to make firm conclusions.

An important intervention, which clinical experience suggests, is beneficial for patients with ALS/MND, is non-invasive ventilation. There may be ethical problems in conducting randomized controlled trials of this in patients with ALS/MND. Bourke et al. performed a randomized controlled trial of non-invasive ventilation in 41 patients with ALS/MND, to assess effects on quality of life and survival. Ninety-two patients participated and were randomly assigned to non-invasive ventilation, or standard care with no ventilation, when they developed orthopnoea with maximum inspiratory pressure <60% of predicted, or symptomatic hyperpnoea. They concluded that in patients without severe bulbar dysfunction, non-invasive ventilation improves survival, with maintenance and improvement of quality of life. In patients with severe bulbar impairment, non-invasive ventilation improved sleep-related symptoms, but did not affect survival. They observed that the survival benefit of non-invasive ventilation was much greater than that attributed to riluzole. Problems with non-invasive ventilation which confound clinical study include individual patient compliance, due, for example, to difficulty tolerating a face mask.

Published Cochrane protocols include branched chain amino acids which have not demonstrated efficacy in ALS/MND. Creatine has antioxidant and neuroprotective properties and may enhance mitochondrial function. There was an improvement in the survival of SOD1 transgenic mouse models of ALS/MND. A small pilot study of 20 ALS/MND patients suggested a beneficial effect on arm strength, but randomized controlled trials of 175 patients, and of 104 patients showed no benefit. A more detailed review of these trials is needed.

Related to the effect of riluzole on possible excitotoxic causes of ALS, modulation of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) was considered, using the GABA modulator gabapentin or GABA agonist gabapentin. No beneficial effect of gabapentin was demonstrated in a randomized controlled trial of 204 patients with ALS, taking a does of 3600 mg gabapentin or placebo, daily, for 9 months.

Lithium is currently topical as a potential treatment for ALS/MND. This follows the publication of a delay in disease onset, duration and extension of life span in the SOD1 transgenic mouse. Feng et al. also reported a delay in disease onset and survival of the mice with lithium, with further benefit from additional valproic acid. Fornai et al. claimed a delay in disease progression in ALS/MND patients taking a daily dose of lithium leading to a plasma level of 0.4–0.8 mEq/l. Specifically, none of the 16 patients treated with lithium and riluzole died in the 15-month period reported, but 8 of the 28
patients treated with riluzole alone died. Other markers of disease progression were also reduced in the patients taking lithium. There have been a number of criticisms of the interpretation of this study, and further studies are underway.

Some caution is needed in the pursuit of clinical trials in ALS/MND as illustrated by a randomized controlled trial of minocycline. Minocycline has anti-apoptotic and anti-inflammatory effects, and extended survival of the SOD1 transgenic mouse model of ALS/MND. Four hundred and twelve patients were studied for 9 months. There was a more rapid deterioration of ALSFRS-R score in treated patients, and the authors concluded that minocycline has a harmful effect on patients with ALS/MND. The interpretation of the results is probably more complex, requiring consideration of optimal dosage and interactions with other medication, in particular riluzole. This also illustrates a recurrent theme of potential medication being reported as effective in the SOD1 mouse model of ALS/MND, but not in people with ALS/MND. Scott et al. repeated many of the reported studies in the SOD1 (G93A) mouse and found no survival benefit (including riluzole). There may be many explanations for this, including the appropriateness of the model, but also the quality of the reported animal studies, which show much of the variable quality, including problems with numbers, blinding and randomization. Guidelines for preclinical ALS/MND therapeutic studies in these mice have been proposed. Similar problems are present in many of the published human studies.

Other online sources of information on treatment for ALS

There are a wide range of other sources of information on management of patients with ALS/MND. In particular, the European Federation of Neurological Societies task force and the EALSC Working Group have produced European guidelines, and the American Academy of Neurology ALS Practice Parameters are helpful documents. NHS Evidence, through Health Information Resources (formerly the NHS National Library for Health) (www.library.nhs.uk), provides access to evidence-based reviews, including the Cochrane Library. Through NHS Evidence—Neurological Conditions (formerly the Neurological Conditions Specialist Library) (www.library.nhs.uk/neurological), it provides access to guidelines, systematic review and research including ‘The medical management of motor neurone disease—a UK perspective of current practice’ and ‘Guidelines for the management of motor neurone disease’ published by the Association of British Neurologists. Also ‘Guidance on the use of riluzole (Rilutek)’ for the treatment of...
motor neurone disease’ published by the National Institute of Clinical Excellence (NICE) (www.nice.org.uk).

**Conclusion**

This is not an exhaustive review of all clinical trials in ALS/MND and other MNDs, but through the methods of the Cochrane Review, detailed reviews of randomized controlled trials are readily available and updated. Riluzole remains the only medication to have shown benefit which has stood up to the methodology of the Cochrane review process. The lack of follow on clinical studies of riluzole in ALS/MND is disappointing, and the true effect remains difficult to define. Many of the medications which most clinicians would consider to be effective, including treatment for sialorrhoea, PEG feeding and assisted ventilation, may not be amenable to randomized controlled trials due to ethical reasons, resources and prioritization. Expert-based guidelines may be helpful in providing suggestions for appropriate practice.

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**References**


