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Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease (Review)

Ng L, Khan F, Young CA, Galea M

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TABLE OF CONTENTS

[Overview of Reviews]

Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease

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ABSTRACT

Background

Motor neuron disease (MND), which is also known as amyotrophic lateral sclerosis (ALS), causes a wide range of symptoms but the evidence base for the effectiveness of the symptomatic treatment therapies is limited.

Objectives

To summarise the evidence from Cochrane Systematic Reviews of all symptomatic treatments for MND.

Methods

We searched the *Cochrane Database of Systematic Reviews* (CDSR) on 15 November 2016 for systematic reviews of symptomatic treatments for MND. We assessed the methodological quality of the included reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) tool and the GRADE approach. We followed standard Cochrane study (review) selection and data extraction procedures. We reported findings narratively and in tables.

Main results

We included nine Cochrane Systematic Reviews of interventions to treat symptoms in people with MND. Three were empty reviews with no included randomised controlled trials (RCTs); however, all three reported on non-RCT evidence and the remaining six included mostly one or two studies. We deemed all of the included reviews of high methodological quality.

Drug therapy for pain

There is no RCT evidence in a Cochrane Systematic Review exploring the efficacy of drug therapy for pain in MND.

Treatment for cramps

There is evidence (13 RCTs, N = 4012) that for the treatment of cramps in MND, compared to placebo:

- memantine and tetrahydrocannabinol (THC) are probably ineffective (moderate-quality evidence);

- vitamin E may have little or no effect (low-quality evidence); and

- the effects of L-threonine, gabapentin, xaliproden, riluzole, and baclofen are uncertain as the evidence is either very low quality or the trial specified the outcome but did not report numerical data.

The review reported adverse effects of riluzole, but it is not clear whether other interventions had adverse effects.

Treatment for spasticity

It is uncertain whether an endurance-based exercise programme improved spasticity or quality of life, measured at three months after the programme, as the quality of evidence is very low (1 RCT, comparison "usual activities", N = 25). The review did not evaluate other approaches, such as use of baclofen as no RCTs were available.

Mechanical ventilation for supporting respiratory function

Non-invasive ventilation (NIV) probably improves median survival and quality of life in people with respiratory insufficiency and normal to moderately impaired bulbar function compared to standard care, and improves quality of life but not survival for people with poor bulbar function (1 RCT, N = 41, moderate-quality evidence; a second RCT did not provide data). The review did not evaluate other approaches such as tracheostomy-assisted ('invasive') ventilation, or assess timing of NIV initiation.

Treatment for sialorrhoea

A single session of botulinum toxin type B injections to parotid and submandibular glands probably improves sialorrhoea and quality of life at up to 4 weeks compared to placebo injections, but not at 8 or 12 weeks after the injections (moderate-quality evidence from 1 placebo-controlled RCT, N = 20). The review authors found no trials of other approaches.

Enteral tube feeding for supporting nutrition

There is no RCT evidence in a Cochrane Systematic Review to support benefit or harms of enteral tube feeding in supporting nutrition in MND.

Repetitive transcranial magnetic stimulation

It is uncertain whether repetitive transcranial magnetic stimulation (rTMS) improves disability or limitation in activity in MND in comparison with sham rTMS (3 RCTs, very low quality evidence, N = 50).

Therapeutic exercise

There is evidence that exercise may improve disability in MND at three months after the exercise programme, but not quality of life, in comparison with "usual activities" or "usual care" including stretching (2 RCTs, low-quality evidence, N = 43).

Multidisciplinary care

There is no RCT evidence in a Cochrane Systematic Review to demonstrate any benefit or harm for multidisciplinary care in MND.

None of the reviews, other than the review of treatment for cramps, reported that adverse events occurred. However, the trials were too small for reliable adverse event reporting.

Authors' conclusions

This overview has highlighted the lack of robust evidence in Cochrane Systematic Reviews on interventions to manage symptoms resulting from MND. It is important to recognise that clinical trials may fail to demonstrate efficacy of an intervention for reasons other than a true lack of efficacy, for example because of insufficient statistical power, the wrong choice of dose, insensitive outcome measures or inappropriate participant eligibility. The trials were mostly too small to reliably assess adverse effects of the treatments. The nature of MND makes it difficult to research clinically accepted or recommended practice, regardless of the level of evidence supporting the practice. It would not be ethical, for example, to design a placebo-controlled trial for treatment of pain in MND or to withhold multidisciplinary care where such care is available. It is therefore highly unlikely that there will ever be classically designed placebo-controlled RCTs in these areas.

We need more research with appropriate study designs, robust methodology, and of sufficient duration to address the changing needs-of people with MND and their caregivers-associated with MND disease progression and mortality. There is a significant gap in studies assessing the effectiveness of interventions for symptoms relating to MND, such as pseudobulbar emotional lability and cognitive and behavioural difficulties. Future studies should use appropriate outcome measures that are reliable, have internal and external validity, and are sensitive to change in what is being measured (such as quality of life).

PLAIN LANGUAGE SUMMARY

Managing symptoms in motor neuron disease

Review question

What are the effects of treatments for managing symptoms in motor neuron disease (MND)?

Background

Motor neuron disease (MND), which is also known as amyotrophic lateral sclerosis (ALS), is an uncommon, incurable disease that affects the nerves involved in movement. MND gets worse over time and affects muscles of the limbs, speech, swallowing and breathing. People with MND experience a wide range of symptoms, including a number of physical ability limitations, pain, spasticity, cramps, swallowing problems and difficulty breathing. It is important to recognise that clinical trials may fail to show that a treatment is effective for several reasons that are not related to the effects of the treatment itself, for example when there are too few people in a trial, or investigators choose an ineffective dose of a drug.

Review characteristics

We searched for Cochrane Systematic Reviews of treatments aiming to manage symptoms of MND. We found nine reviews that fitted the objectives of this study. These reviewed randomized controlled trials (RCTs) of treatments for pain, cramps, spasticity, and sialorrhoea, and assessed the effects of mechanical ventilation (non-invasive ventilation), enteral tube feeding, repetitive transcranial magnetic stimulation (rTMS), therapeutic exercise, and multidisciplinary care. The trials compared the treatment with an inactive treatment (placebo drug or sham therapy) or usual care.

Key results and quality of the evidence

There are currently many treatments in clinical use for pain, but no robust information currently exists on their effectiveness in people with MND.

There is evidence that memantine and tetrahydrocannabinol are probably ineffective for cramps in ALS and that vitamin E may be ineffective. There is too little information from RCTs on the effects of other treatments studied, including L-threonine, gabapentin, xaliproden, riluzole, and baclofen. The review did not report adverse events other than for riluzole.

It is uncertain whether exercise improves muscle stiffness (spasticity). Exercise may improve disability; it may not improve quality of life. Other interventions for spasticity have not been studied in RCTs.

Non-invasive mechanical ventilation probably improves survival and quality of life in ALS; it may not improve survival in people with poor bulbar function. The review did not assess when to start NIV.

A single session of botulinum toxin injections into the salivary glands probably improves excessive saliva production and dribbling, and quality of life in the short term (over weeks but not months).

At present, there is no evidence available from controlled trials to indicate whether or not there is a benefit to tube feeding for supporting nutrition, nor is there any evidence to indicate whether multidisciplinary care is helpful or harmful. It is uncertain whether rTMS is of benefit for improving disability or activity limitation in MND. Lack of evidence on multidisciplinary care or other treatments, however, should not be interpreted as ineffectiveness.

Only the cramps review reported that adverse events occurred. The trials were mostly too small to reliably assess adverse events or rule out uncommon events.

More research is required to determine which treatments help to manage symptoms for those living with MND, using suitable types of studies and outcome measures.

This overview is up to date to November 2016.

BACKGROUND

Description of the condition

Motor neuron disease (MND), which is also known as amyotrophic lateral sclerosis (ALS), is an uncommon, fatal neurodegenerative disorder of the motor system in adults. It has a reported population incidence of between 1.5 and 2.5 per 100,000 person-years worldwide, with the only established risk factors being age and family history (Turner 2007), and possibly military deployment (Beard 2016). Several known genetic changes, such as the pathological hexanucleotide repeat expansion in C9ORF72 (DeJesus-Hernandez 2011; Renton 2011), have been causally associated with familial and sporadic ALS. The disease occurs throughout adult life, with the peak incidence between 50 and 75 years of age, and is more common in men (in the ratio 3:2) (Turner 2007). Historically, ALS was identified as a clinical syndrome distinguishable from other motor neuron diseases such as primary lateral sclerosis, primary muscular atrophy, and progressive bulbar palsy, based upon the location of first symptom and the extent to which anterior horn cells or corticomotor neurons are initially involved. However, it is increasingly evident that ALS is clinically and pathophysiologically diverse, with clear overlap with frontotemporal dementia where there is early loss of frontotemporal system neurons (Turner 2013). Death (usually from respiratory failure) follows on average two to four years after onset, but some people with MND may survive for a decade or more (Forsgren 1983).

Whilst the aetiology of MND is unknown, current evidence suggests that multiple interacting factors contribute to motor neuron injury in MND. The working hypothesis is that MND, like many other chronic diseases, is a complex genetic condition and the relative contribution of individual environmental and genetic factors is likely to be small (Al-Chalabi 2013). The three key pathogenetic hypotheses invoke genetic factors, oxidative stress and glutamatergic toxicity, which result in damage to critical target proteins, such as neurofilaments, and organelles such as mitochondria (Brown 1995; Cookson 1999; Shaw 1997). In addition, there is increasing evidence supporting the hypothesis that altered ribonucleic acid (RNA) processing and aggregation of abnormal proteins play a major role in the pathogenesis of MND (Kim 2013; Verma 2013).

The diagnosis of MND is clinical and includes the presence of upper motor neuron and lower motor neuron signs, progression of disease and the absence of an alternative explanation. There is no single diagnostic test at present that can confirm or entirely exclude the diagnosis of MND. Clinicians rely mainly on clinical history and examination, supported by electrodiagnostic studies (Eisen 2001), and negative findings in neuroimaging and laboratory studies.

The symptoms in MND are diverse and challenging for both the person with MND and the clinician. They include weakness, spasticity, limitations in mobility and activities of daily living, communication deficits, dysphagia, respiratory compromise, fatigue, sleep disorders, pain and psychosocial distress. The International Classification of Functioning, Disability and Health (ICF) defines a common language for describing the impact of disease at different levels: impairment (body structure and function) and limitation in activity and participation (WHO 2001). Within this framework MND-related impairments (weakness and spasticity), can limit 'activity' or function (mobility, self-care) and 'participation' (driving, employment, family and social reintegration). 'Contextual factors' that may be environmental (extrinsic) or personal (intrinsic) interact with all the other constructs to shape the impact of MND on people with the condition and their families.

The burden of disease and economic impact of MND upon people who have the condition, their caregivers (often family members) and on society is substantial (Klein 1996; MND Australia 2015). It is estimated that the per person cost of MND in Australia in 2015 was AUD 1.1 million with a total cost of MND in the country of AUD 2.37 billion, comprising AUD 430.9 million in economic costs and AUD 1.94 billion in burden of disease costs (MND Australia 2015). A study of Australian people with MND in the community (N = 44) showed that despite most requiring a significant amount of help (more than three times a day) (Ng 2011), a quarter of these people received assistance solely from family. It is therefore not surprising that primary caregivers have been estimated to spend a mean of 9.5 hours a day caring for a person with MND, even where there is paid assistance (Chio 2006).

At present, there are few approved drugs for the treatment of MND. Riluzole is the only approved drug treatment for MND in the United States, Australia and in many European countries. It is thought to prolong median survival by about two to three months at one year (Miller 2012). Edaravone, an antioxidant free radical scavenger that is believed to relieve the effects of oxidative stress, is licensed in Japan and currently under consideration in the United States (ALS 2016). In addition, non-invasive ventilation is also thought to prolong survival (Bourke 2006). In the absence of

a cure or indeed any medical intervention which might stop the progression of MND, the focus is on symptomatic, rehabilitative, and palliative therapy with an overall aim of optimising quality of life (QoL).

There are nine reviews in the Cochrane Library that address the effectiveness of a wide range of symptomatic treatment therapies for people with MND (Ashworth 2012; Baldinger 2012; Brettschneider 2013; Dal Bello-Haas 2013; Fang 2013; Katzberg 2011; Ng 2009; Radunovic 2013; Young 2011). This overview draws together the findings from these reviews to make the information more accessible.

Description of the interventions

This review provides an overview of symptomatic treatments for people with MND. Therefore, reviews of therapies that can alter symptoms but which do not target the processes underlying MND are included. Therapies include those that target MND at the impairment level, such as mechanical ventilation for respiratory insufficiency, enteral feeding for maintenance of nutrition impairment, and treatments for spasticity, sialorrhoea, cramps and pain; and those that target MND at the level of activity and participation, such as multidisciplinary care, repetitive transcranial magnetic stimulation (rTMS) and therapeutic exercise.

How the intervention might work

A wide range of interventions is used to treat the diverse symptoms and impairments in MND. At the level of impairment, interventions include the following:

- Mechanical ventilation (tracheostomy and non-invasive ventilation) might prolong survival and optimise QoL by supporting ventilation in those with clinically significant respiratory muscle weakness.
- Enteral feeding might improve weight maintenance, survival, and QoL by providing a safe and reliable route for nutrition in people with MND who may have a combination of dysphagia, poor appetite, and impaired ability to feed themselves leading to reduced oral intake and malnutrition/dehydration.
- Spasticity treatments vary widely and may include physiotherapy (for example, therapeutic exercises, stretching, positioning), modalities (for example heat, cold, vibration, electrical stimulation), prescription medication (for example baclofen), non-prescription medication (for example vitamins), chemical neurolysis (botulinum toxin), surgical interventions (for example intrathecal pumps) and alternative therapies (for example reflexology). How the interventions might work varies widely from one intervention to another. Most commonly, stretching techniques are used in combination with one or more 'true' muscle relaxants (such as baclofen) (Carter 1998), and such interventions work by lengthening (with or without the assistance of weakening) the agonist muscle.
- Sialorrhoea treatments include suction, drug treatments and more invasive approaches, such as injection of botulinum toxin or irradiating the salivary glands, which may improve sialorrhoea and QoL. These interventions work by reducing the amount of saliva either through its removal (for example, by suction) or reduction of salivary output (for example, by anticholinergic medications and botulinum toxin injections).
- Cramps - as the origin of cramps is poorly understood, so too are the mechanisms of treatment. Two different pathophysiological mechanisms have been proposed: abnormal excitation of the terminal branches of motor axons (Bertolasi 1993), and hyperexcitability or bistability of motor neurons at a spinal level (Baldissera 1994). The aetiology of cramps in MND and the mechanism of action of treatments remains uncertain.
- Pharmacological pain management works by reducing pain. However, analgesics work on different pathways. For example, paracetamol and non-steroidal anti-inflammatory drugs inhibit the production of pain by inhibiting the production of prostaglandins, whilst opiates (such as morphine) imitate natural neuromediators by binding their receptors (such as endorphin receptors).

At the level of activity and participation, interventions include the following:

- Multidisciplinary care might reduce disability and improve QoL by applying "a problem-solving education process" (Wade 1992), delivered by medical and allied health disciplines (such as physiotherapy, occupational therapy, and speech therapy) that are focused on maximising activity and participation.
- Transcranial magnetic stimulation might stimulate nerve cells in superficial areas of the brain by applying a high-energy magnetic field at the skull surface which induces a perpendicular electrical field in the vertical plane through the cortex. It might provide a non-invasive approach to condition the excitability and activity of neurons (Kobayashi 2003), and at low frequency (equal to or less than 1 Hz), bring a reduction in glutamate-induced excitotoxicity, which may improve motor function in MND (Ziemann 2004). At higher frequency (faster than 1 Hz), it is thought that the increased expression of neurotrophic factors could be neuroprotective (Angelucci 2004).
- Exercise might reduce disability and fatigue and improve QoL by improving cardiovascular deconditioning and disuse weakness.

Why it is important to do this overview

Nine published Cochrane Systematic Reviews in the Cochrane Library address the effectiveness of a wide range of symptomatic treatment therapies for people with MND specifically. This overview draws together the findings from multiple Cochrane in-

tervention reviews to give clinicians, policy makers and informed consumers a 'friendly front end' for data from a wide range of reviews. This has the benefit of both making the information more accessible and highlighting areas that need further research.

OBJECTIVES

To summarise the evidence from Cochrane Systematic Reviews of all symptomatic treatments for motor neuron disease (MND).

METHODS

Criteria for considering reviews for inclusion

Types of reviews

As per Chapter 22 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Becker 2011), we considered all Cochrane Systematic Reviews for all treatments for motor neuron disease (MND). These systematic reviews have the following characteristics:

- pre-defined objectives;
- pre-defined criteria for eligibility of evidence;
- an objective systematic search for evidence applying predetermined inclusion and exclusion criteria; and
- explicit and systematic methods for synthesising evidence, which attempt to reduce bias.

We did not consider non-Cochrane Systematic Reviews or non-systematic reviews for inclusion. Where a systematic review included both MND and non-MND populations we included the systematic review if the review reported results for people with MND separately.

Types of participants

We included all forms of MND, regardless of clinical pattern (for example bulbar or limb onset). In participants with amyotrophic lateral sclerosis (ALS), we used the El Escorial and revised El Escorial criteria (Brooks 1994; Brooks 2000).

Types of interventions

We included all non-disease modifying and symptomatic interventions for MND, whether pharmacological or physical. We did not include treatments that target the underlying disease process in MND. These are the subject of a parallel overview of reviews on disease modifying therapies in MND, which is in development.

Types of outcomes

In the narrative part of our overview, we report the outcomes reported in the individual Cochrane Systematic Reviews. Where possible, we categorised outcomes according to the International Classification of Functioning, Disability and Health (ICF) (WHO 2001) into those that focused on:

- impairment - for example, forced vital capacity (FVC);
- disability or limitation in activity - for example, the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (the domains of ALSFRS include speech, salivation and swallowing; turning in bed, walking, climbing stairs; dressing and hygiene, handwriting, cutting food; and respiratory insufficiency, dyspnoea, orthopnoea);
- restriction in participation, and environmental or personal context, or both - for example, mood of the person with MND and their caregiver, satisfaction with services, social integration.

Many of the scales above predate the introduction of the concepts of the ICF domains. The outcome measures often cross boundaries between the concepts of impairment, disability and participation. For example, ALSFRS lists impairments such as dyspnoea and orthopnoea, as well as disabilities such as walking or climbing stairs. Other important outcomes, such as survival and QoL, are not strictly covered by the ICF concepts (although there is again cross-over of boundaries between ICF concepts and these outcomes). Nevertheless, the ICF provides an important framework, which allows the use of a common standardised language worldwide, hence its application in this overview. Scales used must have been validated as having good reproducibility, face validity and correlation with other scales measuring the same attribute. Outcomes were divided into short-term (up to 3 months), medium-term (3 to 12 months) and long-term (at least 12 months) time points, for both primary and secondary outcomes.

Primary outcomes

Primary outcomes focus on domains within QoL and health status after 12 months, such as the Short Form-36 (SF-36) or Visual Analogue Scale (VAS) on life satisfaction and well-being. As QoL is a broad concept, it could be measured by a broad range of scales measuring various aspects of QoL.

Secondary outcomes

These include the following short-term, medium-term and long-term outcomes:

- outcomes that relate to impairment - for example, forced vital capacity (FVC);
- outcomes that relate to disability or limitation in activity - for example, Amyotrophic Lateral Sclerosis Severity Scale (ALSSS) and ALSFRS;

- outcomes that relate to restriction in participation, and environmental or personal context, or both - for example, Caregiver Strain Index (CSI), Utrecht Coping List (UCL);
- survival;
- hospitalisation such as readmissions and hospital length of stay (LOS); and
- cost-effectiveness of care.

We reported adverse events that may have resulted from the intervention, as defined as events that were fatal, life-threatening, or required hospitalisation. We also reported side effects from drugs. This review assesses treatments for a range of symptoms. Not all outcomes are relevant to all treatments in an overview of this sort. We have reported outcomes where measured but not commented where outcomes were not relevant to the intervention in question.

Search methods for identification of reviews

In November 2016, we searched the *Cochrane Database of Systematic Reviews* (CDSR) for Cochrane Systematic Reviews of MND.
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The search strategy is in Appendix 1.

Data collection and analysis

Selection of reviews

Two overview authors (LN and FK) selected systematic reviews for inclusion and resolved disagreements by consensus following discussion with a third overview author (MG).

Data extraction and management

Two overview authors (LN and FK) independently collected data from published systematic reviews with a data collection form designed to include all the data needed. We used 'Characteristics of included reviews' tables to present the essential features of the included reviews.
We resolved disagreements by consensus following discussion with a third author (MG).
We contacted the review authors or extracted data from the relevant trials if further information was required.
We extracted the following characteristics from the reviews:
- date assessed as up to date;
- objectives;
- participants;
- interventions;
- comparisons;
- outcomes in the review for which data are available; and
- limitations.

Assessment of methodological quality of included reviews

Two overview authors, at least one of whom was not an author of the original included reviews, independently assessed the methodological quality of each review included in the overview. For this purpose we used the Assessment of Multiple Systematic Reviews (AMSTAR) tool (Table 1) developed by Shea 2007, which has acceptable inter-rater agreement, construct validity and feasibility (Shea 2009). Two overview authors (LN and FK) also independently assessed the quality of the evidence in the included reviews with the GRADE approach (Guyatt 2008). In both cases, we resolved disagreements by discussion, if necessary with a third author (MG).

Data synthesis

We present data predominantly as a narrative review. We report the evidence for each intervention from each review and its strength in an 'Overview of reviews' table using the GRADE approach. We used the following criteria to assess the quality of the evidence: study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness, and publication bias. We assessed the evidence using GRADE criteria where reviews lack 'Summary of findings' tables. We present data by symptom.
In 'Overview of reviews tables' we present:
- beneficial and harmful outcomes;
- frequency or severity of these outcomes in the control groups;
- estimates of the relative and absolute effects of the interventions;
- indications of the risk of bias (which may vary by outcome and comparison); and
- comments.

Where we found more than one eligible review of a particular intervention and the conclusions agreed, we report this; where the conclusions differed, we further explored this, taking into account the AMSTAR scores of the included reviews.
Due to the heterogeneity of the included systematic reviews, it was not possible to perform statistically valid direct or indirect comparisons on the interventions contained within this overview.

RESULTS

Description of included reviews

We identified 82 Cochrane Systematic Reviews in the *Cochrane Database of Systematic Reviews* (CDSR). Of these, 30 passed the first screening review and were selected for closer scrutiny. We excluded 18 reviews (Table 2); three others were reviews in palliative

care conditions but did not have content relating specifically to motor neuron disease (MND); hence we included nine reviews (Table 3).

The nine included reviews address the effectiveness of a range of symptomatic treatment therapies for people with MND at both the level of impairment and at the level of activity and participation. At the level of impairment, interventions included: drug therapy for pain (Brettschneider 2013), treatment for cramps (Baldinger 2012), treatment for spasticity (Ashworth 2012), mechanical ventilation for supporting respiratory function (Radunovic 2013), treatment for sialorrhoea (Young 2011), and enteral tube supporting nutrition (Katzberg 2011). At the level of activity and participation, interventions included rTMS (Fang 2013), therapeutic exercise (Dal Bello-Haas 2013), and multidisciplinary care (Ng 2009).

Methodological quality of included reviews

See Table 4 for methodological quality of the reviews and Table 5 for methodological quality of studies within included systematic reviews.

All the included reviews achieved an Assessment of Multiple Systematic Reviews (AMSTAR) rating of either 10 or 11 out of 11 (Shea 2007), and we deemed them of high methodological quality. There were three 'empty' reviews (Brettschneider 2013; Katzberg 2011; Ng 2009), defined as reviews with no included studies. For these reviews, a number of criteria were not applicable (characteristics of included studies provided; scientific quality of included studies assessed and documented; scientific quality of included studies used appropriately in formulating conclusions; appropriate methods used to combine study findings; likelihood of publication bias; conflict of interest stated for both the systematic review and included studies). None of the reviews that contained included studies scored a point for "Conflict of interest stated for both the systematic review and included studies". Whilst all the reviews clearly stated conflicts of interest for the review, none reported conflict of interest for included studies within the review.

For all reviews with included studies, at least two review authors independently assessed the risk of bias in each study using the same tools. The review authors considered risk of bias for seven methodological domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome reporting, selective outcome reporting and other sources of bias. We assessed these domains according to the *Cochrane Handbook for Systematic Reviews of Interventions*. We judged each of the criteria relating to the risk of bias as 'low risk', 'high risk' or 'unclear risk' and we resolved any disagreements through discussion with a third author.

In Table 5 'Overview of reviews', we reported the evidence for each intervention from each review and its strength using the GRADE approach, using the criteria of study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness, and publication bias. In the reviews where the review authors had used GRADE to determine the strength of the evidence for each intervention, we reassessed the grading of evidence where we felt that a different grade would more accurately reflect the level of evidence. For example, in the review for treatment for cramps, the review authors judged studies with very small sample sizes (underpowered to detect an effect) but otherwise at low risk of bias to be of moderate quality. We downgraded them to low quality in this overview. Where the strength of evidence was based on a single study alone with a low risk of bias, we decided that the quality of evidence could at best be moderate and not high.

Effect of interventions

Interventions at the level of impairment

Drug therapy for pain

In the Cochrane Systematic Review by Brettschneider 2013, the review authors found no randomised controlled trials (RCTs) or quasi-RCTs on drug therapy for pain experienced as part of motor neuron disease (MND). This was unsurprising given the ethical concerns around designing a placebo-controlled trial for treatment of pain in MND. The review authors therefore considered non-randomised evidence in the form of retrospective case series of more than five participants where people were treated consecutively, and found 13 case studies suggesting that pain occurs in up to 78% of people with MND and that frequency and intensity of pain increases with ongoing disease. Pain was most frequently associated with reduced joint mobility, cramps, or skin pressure caused by immobility. Paracetamol or other non-steroidal anti-inflammatory drugs (NSAIDs) were commonly used as first line treatment. However, in the later stages of disease, opioids were reported as more effective for pain and also had a concurrent beneficial effect on dyspnoea and insomnia. The authors concluded that pain was a common unresolved problem in MND. In the absence of any evidence from RCTs, and utilising non-randomised evidence, they concluded that treatment for pain in MND should follow the 1990 World Health Organization (WHO) Analgesic Ladder (WHO 1990).

Treatment for cramps

Baldinger 2012 identified 13 RCTs (N = 4012), in which interventions for cramps were studied in participants with MND, of which one study (tetrahydrocannabinol) assessed cramps as the primary endpoint. Twelve studies (of vitamin E, baclofen, riluzole, L-threonine, xaliproden, gabapentin, or memantine) assessed cramps as a secondary endpoint. The systematic review also included six studies (of creatine, gabapentin, indinavir, dextromethorphan, quinidine, or lithium) that assessed cramps as an adverse event, but

we did not consider them in this treatment overview. Assessment time points varied widely. The review did not report adverse events from interventions for cramps other than for riluzole; it is unclear whether other trials did not report adverse events or whether no adverse events occurred (see Table 5). Most trials assessed cramps at regular intervals (ranging from weekly to 12-weekly) and one of the studies had a single assessment time point at 12 months. In none of the studies was there a clear benefit from any of the medications. However, many studies were underpowered to draw a definite conclusion. Notably, the review authors identified no studies using physical therapy as a therapeutic intervention for cramps.

Treatment for spasticity

Ashworth 2012 found a single RCT addressing the treatment of spasticity in MND, in which spasticity (as measured by the Ashworth Scale) was improved at 3 months following an endurance-based exercise programme. The study had a very small sample size (N = 25) and was at high risk of bias. Significantly, attrition was high enough to be a "fatal flaw": 30% of participants had been lost at 3 months, 50% at 6 months, and so many at 9 or 12 months that no further analyses could be done. There was no statistically significant improvement in QoL and no adverse events were reported. The review authors concluded that based on this single study, it was not possible to determine whether individualised moderate-intensity endurance-type exercise was beneficial or harmful and that current practice, which includes anti-spasticity drugs such as baclofen and a programme of regular stretching, required more research, especially considering the potential harm from these drugs through worsening muscle weakness and function.

Mechanical ventilation for supporting respiratory function

Radunovic 2013 identified two RCTs involving 54 participants with MND receiving non-invasive ventilation (NIV). The review authors were unable to analyse one of the studies as it had incomplete data (6 out of 13 participants). It also had no clear protocol as it was originally designed as a pilot study and did not receive funding for continuation. Results of the Cochrane Systematic Review were therefore based on a single well-conducted RCT of non-invasive ventilation versus standard care, which was at low risk of bias (N = 41). Outcomes included survival and QoL (measured until at least 12 months or until death). Overall median survival was significantly improved in the NIV group (219 days compared to 171 days for standard care) and the survival benefit was predominantly in the subgroup with normal to moderately impaired bulbar function. NIV also resulted in a benefit in the maintenance of QoL for most of the duration of survival in this subgroup. Whilst NIV did not prolong survival in participants with poor bulbar function, there was a significant improvement in the 'Mean Symptoms' domain of the Sleep Apnoea Quality of Life Index, but not in the Short Form-36 Health Survey Mental Component Summary score. Function was not measured and no adverse events were reported. The authors of the review reported that, given the RCT confirmed previous observational studies, which have shown survival advantage and improved QoL in people with MND who start and can tolerate NIV at the onset of respiratory impairment, ethically it was unlikely that there would be further randomised controlled trials of NIV in unselected cohorts of people with MND. The review did not assess when to start NIV. Additionally, the National Institute for Health and Clinical Excellence has carried out a cost-effectiveness analysis using the Markov Model and concluded that the use of NIV in the management of people with MND represents a cost-effective use of resources (NICE 2010b).

Treatment for sialorrhoea

Young 2011 identified a single RCT relating to treatment of sialorrhoea in MND which involved botulinum toxin type B injections. The results favoured a single session of botulinum toxin type B injections to parotid and submandibular glands, which produced both subjective and objective benefits in people with MND for up to 4 weeks. However, effects appeared to be lost by 8 to 12 weeks. Other than the relatively small sample size (N = 20), the study was methodologically robust (randomisation and analysis appeared good and data completeness was satisfactory) and findings were supported by other non-randomised trials (which were included in the discussion); these were typically open label studies on the use of botulinum toxin to reduce saliva production in MND. Although no adverse events were reported in this RCT, serious adverse events such as infection of the salivary gland and dysphagia have previously been reported with this intervention (Winterholler 2001).

Enteral tube feeding for supporting nutrition

Katzberg 2011 did not identify any RCTs that evaluated the efficacy of percutaneous endoscopic gastrostomy (PEG) or other feeding tube placement. There were, however, 11 non-RCTs relating to PEG insertion that the review authors identified and discussed. All 11 studies tested for a possible survival advantage. Two prospective and two retrospective studies reported a longer survival in people with MND (regardless of limb or bulbar onset) after PEG compared to people feeding orally, whilst one prospective and six retrospective studies failed to find a survival advantage. The trial authors noted, however, that the latter studies had multiple design flaws, the major flaw being lack of control for confounders. Katzberg and colleagues concluded that survival advantage was weakly positive. Nutrition was not as rigorously studied, but the three studies that did assess nutrition found a positive outcome for PEG. The studies did not assess QoL effectively and the review authors drew no conclusions about this outcome. In terms

of safety, the frequency of minor complications of PEG tube insertion ranged from 2% to 16% and major complications, mostly comprising PEG failure, occurred in up to 45% of participants. Complications during the procedure itself (including death) were infrequently reported. There was little evidence to guide timing of PEG insertion, with some evidence that PEG insertion may be more risky in people with a forced vital capacity (FVC) less than 50%, but there is also evidence that even people with MND with low FVC may still benefit from PEG placement, particularly when NIV is used during the procedure. Four studies compared the effectiveness and safety of percutaneous radiological gastrostomy (PRG), which is also known as radiologically inserted gastrostomy (RIG), to PEG and found them equally effective with similar rates of complications.

Interventions at the level of activity and participation

Repetitive transcranial magnetic stimulation (rTMS)

Fang 2013 aimed to determine the efficacy of rTMS primarily on disability or limitation in activity. Three studies with small sample sizes (50 participants in total) compared rTMS with sham TMS. There was heterogeneity in the rTMS technique with respect to duration of treatment, frequency of rTMS and intensity of rTMS. Outcome measurement time points also varied widely between the three studies (4 weeks, 6 months, and 12 months). None of the three studies provided detailed data on the ALS Functional Rating Scale-Revised (ALSFRS-R) at six months which was the pre-assigned primary outcome in the review. The trials provided only statistical summary data, with no raw numerical data. Of the two studies that provided statistical summary data on ALSFRS-R at 6 months, the results were conflicting, with one indicating a benefit and the other finding no statistical difference. Little or no difference was seen between rTMS and sham TMS using ALSFRS-R and changes to muscle strength at 12 months. All three studies had significant methodological limitations including lack of information on random sequence generation or on allocation concealment, incomplete outcome data, high attrition and lack of intention-to-treat analyses. None of the trials reported any adverse events associated with the use of rTMS. In view of the significant methodological limitations, the review authors concluded that it would be premature to make any judgement on the short-term or long-term safety of rTMS.

Therapeutic exercise

Dal Bello-Haas 2013 identified two studies on the effects of exercise in people with MND, one of which (Drory 2001), primarily investigated the effect of exercise on spasticity and is therefore also reported in the review for treatment of spasticity (Ashworth 2012). The focus of the exercise differed: one described endurance exercises; the other, resistive exercises. Both trials had small sample sizes (in total 43 participants) and the risk of bias of Dal Bello-Haas 2007 was significantly lower than Drory 2001, which had high attrition (30% at 3 months, with subsequent attrition so significant at 9 and 12 months that analyses could not be completed), no allocation concealment and no blinding. Outcome measures used, however, were similar in both studies and allowed pooling of data, which showed statistically significant improvement in disability (measured by ALSFRS) at 3 months, which was not sustained at 6 months. There were no statistical differences found in QoL, fatigue, or muscle strength and, importantly, no adverse events were reported. In people with MND, the lack of research evidence means that some clinicians discourage strengthening or aerobic exercise programmes. The safe range for therapeutic exercise is dependent on the extent of disease involvement - a weak muscle is more susceptible to overwork damage. This should be balanced, however, with the effects of cardiovascular deconditioning and disuse atrophy. The review authors concluded that the included studies were too small to determine to what extent strengthening exercises for people with ALS are beneficial or harmful. They therefore concluded that further studies are needed to determine the ideal exercise prescription for people with MND, in terms of both which exercise protocols are most beneficial or cause undue risks and whether there is a subset of people with MND who respond more positively to exercise.

Multidisciplinary care

In the systematic review by Ng 2009, the review authors found no randomised or quasi-randomised controlled trials on multidisciplinary care for people with MND. Given the similar ethical concerns around designing such trials for treatment of pain, this was not unexpected. The authors considered observational, cohort and cross-sectional studies with the understanding that contribution of such studies to best evidence synthesis would be limited. The review authors found five low- to very low-quality observational studies that suggested very tentative evidence for QoL (mental health domains) without increasing healthcare costs, reduced hospitalisation (in outpatient settings), and improved disability (in inpatient settings). None of the studies reported any adverse effects attributable to multidisciplinary care. The authors concluded that whilst these findings were tentative, a gap in current research should not be interpreted as proof that multidisciplinary care is ineffective.

DISCUSSION

Summary of main results

This overview draws together the findings from multiple Cochrane Systematic Intervention Reviews to give clinicians, policy makers

and informed consumers a 'friendly front end' for data from a wide range of reviews. It has highlighted the lack of robust evidence on interventions to manage the symptoms resulting from MND. Very few large controlled trials have been undertaken for this condition in terms of symptom management. Three reviews were empty reviews; however, all three reported on non-randomised controlled trial (non-RCT) evidence and the remaining six included mostly one or two studies. One review on treatment for cramps included 20 studies, but many of these studies were not primarily designed to investigate treatment for cramps, the review did not fully report adverse events of these interventions, and seven trials reviewed cramps as adverse events. None of the reviews reported any adverse effects or events as a result of treatment apart from medications for cramps, which reported adverse events of riluzole (but did not report on adverse events of other interventions). Given the lack of robust evidence, it would be premature to judge the treatments as 'safe'. It is important to recognise that clinical trials may fail to show that a treatment is effective for several reasons other than that the drug is ineffective, for example insufficient statistical power, wrong choice of dose, insensitive outcome measures or inappropriate participant eligibility criteria. Therefore, a lack of evidence does not necessarily equate to ineffectiveness and should not override clinical judgement and discussion between a clinician and the person with MND.

By intervention/symptoms:

Comparisons were usual activities, usual care, or a placebo (inactive) treatment.

Interventions at the level of impairment

Drug therapy for pain

There is no evidence for or against any drug therapy for pain for MND.

Treatment for cramps

There is evidence from placebo-controlled trials that tetrahydrocannabinol (THC) and memantine are probably ineffective for the treatment of cramps in MND (moderate-quality evidence) and that vitamin E may have little or no effect (low-quality evidence). The effects of L-threonine, gabapentin, xaliproden, riluzole, and baclofen are uncertain, as the evidence is either very low quality or the trial specified the outcome but did not report numerical data.

Treatment for spasticity

It is uncertain whether an endurance-based exercise programme improves spasticity or quality of life (QoL) at 3 months compared with usual activities. The review did not evaluate other approaches, such as the use of baclofen.

Mechanical ventilation for supporting respiratory function

Non-invasive ventilation (NIV) probably improves median survival and quality of life in people with respiratory insufficiency and normal to moderately impaired bulbar function, compared to standard care, and improves QoL but not survival for people with poor bulbar function.

Treatment for sialorrhoea

A single session of botulinum toxin type B injections to parotid and submandibular glands probably improves sialorrhoea and QoL at up to 4 weeks compared to placebo injections, but not at 8 or 12 weeks. The review did not evaluate other approaches as no trials were available.

Enteral tube feeding for supporting nutrition

There is no RCT evidence for or against enteral tube feeding for supporting nutrition in MND.

Interventions at the level of activity and participation

Repetitive transcranial magnetic stimulation (rTMS)

It is very uncertain whether or not rTMS improves disability or limitation in activity in MND compared to sham rTMS.

Therapeutic exercise

Exercise may improve disability in MND at 3 months but not QoL compared to usual activities or usual care.

Multidisciplinary care

There is no RCT evidence for or against multidisciplinary care in MND.

By outcomes:

Primary outcome - quality of life

The following interventions probably improve QoL in MND:

- NIV for survival;
- botulinum toxin type B injections for treatment of sialorrhoea 4 weeks after treatment.

The following intervention probably does *not* improve QoL:

- botulinum toxin type B injections for treatment of sialorrhoea (moderate-quality evidence) at 8 or 12 weeks.

The following intervention may lead to little or no difference in QoL:

- endurance-based exercise programme for spasticity treatment or resistive exercise programme (low-quality evidence) at 3 months.

It is not known if the following interventions improve QoL:

- drug therapy for pain;
- drug therapy for cramps: THC, memantine, riluzole, vitamin E, L- threonine, gabapentin, xaliproden, riluzole, and baclofen;
- enteral tube feeding for nutrition;
- rTMS;
- multidisciplinary care.

Secondary outcomes

Impairment - refer to individual interventions at the level of impairment above.

Activity and participation as measured by ALSFRS

The following interventions may improve level of activity/reduce disability (low-quality evidence):

- resistive exercise programme at 3 months.

It is uncertain whether or not the following interventions improve level of activity or reduce disability because the quality of evidence is very low:

- endurance-based exercise programme for treatment of spasticity at 3 months;
- rTMS.

It is not known if the following interventions improve level of activity/reduce disability:

- NIV;
- botulinum toxin type B injections for treatment of sialorrhoea;
- drug therapy for pain;
- drug therapy for cramps: THC, memantine, riluzole, vitamin E, L-threonine, gabapentin, xaliproden, riluzole, and baclofen;
- enteral tube feeding for nutrition;
- multidisciplinary care.

Overall completeness and applicability of evidence

This overview sought to determine the efficacy of interventions used for the relief of symptoms at the level of impairment, activity and participation in people with MND. Only Cochrane Systematic Reviews with participants who had MND were included in this overview. Due to the heterogeneity of the interventions, we were unable to perform any mathematical or statistical direct or indirect comparisons across reviews. Two reviews (treatment of spasticity and therapeutic exercise) had an overlap of included studies and there were many other symptoms in MND (such as cognitive and behavioural impairment and pseudobulbar emotional lability), which were not covered at all in this overview. Protocols for Cochrane Systematic Reviews of diaphragm pacing in ALS (Maguire 2014) and treatment of fatigue (Young 2014) have been published and reviews are in development, There was a relative lack of QoL data. Most of the trials were too small for reliable adverse event reporting.

Quality of the evidence

It is current policy for the Cochrane Library to update reviews as new evidence likely to change conclusions emerges. All of the included systematic reviews have been updated within 5 years of publication where there has been such evidence. Conclusions of the reviews are therefore mostly reflective of current research findings. All the systematic reviews were of robust methodological quality although three were empty, hence many of the methodological quality criteria were not applicable and a conclusion is that there is no high-quality evidence for these areas. All included Cochrane Systematic Reviews used a standard quality assessment tool (Cochrane 'Risk of bias' tool), hence there was a uniformity in assessment of bias. Conflicts of interest were clear within the reviews themselves but not routinely reported for the included studies within the included systematic reviews. It would helpful for this information to be presented in the reviews to allow for determination of potential biases in outcomes and conclusions drawn. Updated Cochrane methodology now mandates the reporting of conflicts from primary studies where available.

Of the Cochrane Systematic Reviews with included studies, most had small numbers of studies (usually one or two only) each with small numbers of participants. There was imprecision of the data for measures of effect in many of the trials. High attrition rates were also common and intention-to-treat analysis was not always applied. Blinding of participants was difficult with most of the interventions; and outcome assessors were also often not blinded. Where participants and outcome assessors were clearly blinded (Young 2011), by 12 weeks 70% of investigators and 90% of participants guessed treatment allocation correctly, suggesting that despite excellent attempts to maintain blinding, the double-blind was not preserved. Regardless, the methodological quality of almost all the studies could have been improved with blinding of outcome assessors. Additionally, there was significant heterogeneity of intervention within each review and outcomes also varied widely. None of the studies addressed cost-benefits, nor the role of caregivers and their needs.

Potential biases in the overview process

All overviews are limited by the risks of bias of the included Cochrane Systematic Reviews and their included studies. We limited systematic review inclusions and extraction of data to Cochrane Systematic Reviews. It is possible that the Cochrane Systematic Reviews may not have sought unpublished or ongoing studies via trials' registries as this was not standard practice at the time of publication of many of these reviews. We did not seek additional information from authors of the included studies. The high Assessment of Multiple Systematic Reviews (AMSTAR) scores for the Cochrane reviews were reassuring for the quality of the reviews. However, the use of GRADE criteria introduced an element of subjective judgement although this is now widely accepted as a quality tool. It was made more challenging as the overview primarily assessed the included reviews rather than the original studies, and review authors may assess and report study quality in different ways. Judgement can be open to interpretation. We made the decision to downgrade studies twice based on small sample sizes, inadequately powered to detect an effect, which was harsher than the decision of the authors of the original reviews. We also decided that a single, albeit high-quality, study at low risk of bias was at best able to provide moderate-quality evidence where further research still had a likelihood of changing the estimate of effect.

LN, FK and CY are authors of included systematic reviews. Two overview authors, at least one of whom was not an author of the original included reviews, independently assessed the methodological quality of each review included in the overview.

Agreements and disagreements with other studies or reviews

To the best of our knowledge, there are no other systematic overviews on interventions to manage symptoms in people with MND. Evidence-based practice for MND should include a) integration of best available scientific evidence, b) clinical expertise, judgement, and agreement, and c) the incorporation of the values and beliefs of people with MND. There is currently a gap between the available evidence, clinical practice, and agreement between clinicians and incorporation of patient values in the treatment of people with MND (Cicerone 2005).

Whilst RCTs remain the 'gold standard' for determining the effectiveness of interventions, concerns have been raised about the application of RCTs in complex interventions such as rehabilitation or multidisciplinary care (Cicerone 2005). For such complex interventions, an alternative to RCTs may be the use of an observational approach - the Practice Clinical Trial or Clinical Practice Improvement (CPI) method that acquires prospective or retrospective data without disrupting the natural milieu of treatment (Gassaway 2005). These types of studies, however, are not generally included within Cochrane reviews. Cochrane Systematic Reviews that in the future include non-randomised evidence, graded for quality, may add to the volume of evidence in this overview, but may make quality judgements harder.

Even with the study of effects of simple interventions or discrete outcomes where RCTs are best suited, there are a number of logistical and ethical reasons that makes treatment in MND particularly challenging to study. MND is a relatively rare condition, heterogenous in clinical presentation and manifestations, and results in a rapidly disabling population with high mortality rates. People with MND often prefer to participate in disease-modifying pharmaceutical trials that might slow disease progression over other trials (Dal Bello-Haas 2007). Attrition is particularly common, especially in trials requiring longer follow-up, as participants may have difficulty attending clinic for follow-up due to respiratory and mobility issues, rapid disease deterioration resulting in mechanical ventilation or death, long distances to travel to the clinic for follow-up, and fatigue (Drory 2001).

Because of the nature of MND, it is also difficult to research clinically accepted or recommended practice, regardless of the level of evidence supporting the practice. It would not be ethical, for example, to design a placebo-controlled trial for treatment of pain in MND or to withhold multidisciplinary care where such care is available. It is, therefore, highly likely that there will never be RCTs available in these areas. Similarly, where there is some evidence of benefit from a single RCT, such as in NIV, it is unlikely that further RCTs of NIV in unselected cohorts of people with MND would occur. Even when there are no RCTs available but there is non-RCT evidence showing weak survival advantage, such as in the case of enteral tube feeding, it is probably unlikely that RCTs will be conducted. Regardless of the evidence available, local practices also vary considerably, for cultural, financial or other reasons. Assisted ventilation for example can be provided with invasive (tracheostomy ventilation) or non-invasive means. Whilst tracheostomy ventilation in MND is not encouraged in Europe and North America (Borasio 2001; Yamaguchi 2001), it is the predominant form of ventilation offered to people in Japan, where the cost is fully covered by the government and medical insurance (Kawata 2008).

Another issue relating to clinical trials is the choice of outcome measures. Due to the widespread use of ALSFRS-R, when outcomes at the level of activity limitation are measured, trials commonly use ALSFRS-R, which allows for pooling of data. QoL is an important outcome measure for people with MND. QoL is a broad concept however, and it is not easily incorporated in a single quantitative statistically valid outcome measurement. Furthermore the measurement has no anchor and people with MND often report a high QoL, persisting throughout their disease due to shifting expectations and to reprioritisation factors contributing to QoL (Simmons 2015). Many outcome measures for health-related QoL are generic (e.g. SF-36), not fully validated for MND and limited by floor effects (Jenkinson 2002; Young 1995). Although measures specific for MND, such as the ALSAQ-40, have

since been developed for use, they have yet to be widely taken up. Some are heavily weighted towards physical function (e.g. ALSAQ-40) and do not include an existential element (perception of purpose, meaning of life, capacity for personal growth) relevant for persons with MND (Bromberg 2008). Other measures in this population include the direct-weight version of the Schedule of the Evaluation of Individual Quality of Life (SEIQoL-DW) (Hickey 1996), which can be used for both people with MND and their caregivers, but this scale is time intensive (Mountain 2004), and does not allow comparison between people. The World Health Organization (WHO) pioneered the development of QoL measures with a more global view (WHOQOL and WHOQOL-BREF) (WHOQOL 1998a; WHOQOL 1998b). More recently, a modified version of the McGill questionnaire, which also has more global elements, was validated as an ALS-specific QoL questionnaire (the ALSSQOL) (Simmons 2006), and a shortened version (ALSSQOL-R) has been validated through multicentre study (Felgoise 2007). In general, the overall self-perceived well-being of a person with MND is determined by wide-ranging factors including physical, psychological, existential, religious, and financial, etc. and a global instrument such as WHOQOL-BREF, SEIQoL-DW, or ALSSQOL-R may be used (Simmons 2015). When assessing the impact of a very specific therapeutic intervention, however, global QoL instruments will likely be insensitive and therefore a more specific instrument that is based on health-related QoL should be chosen (Simmons 2015). For example, NIV improves sleep quality but as the person deteriorates in health, they may experience loss of relationships or financial difficulties which would affect global QoL. Not surprisingly, therefore, it was found that NIV improved Sleep Apnoea Quality of Life Index but not SF-36.

AUTHORS' CONCLUSIONS

Implications for practice

The limitations of the evidence base mean that absence of proof for the following treatments *cannot* be interpreted as proof that they are ineffective.

Drug therapy for pain

Pain is a common unresolved problem in motor neuron disease (MND) and in the absence of any evidence from randomised controlled trials (RCTs), treatment for pain in MND could follow the 1990 World Health Organization Analgesic Ladder (WHO 1990).

Treatment for cramps

Cramps can cause pain and impair function. There is some evidence of lack of efficacy for tetrahydrocannabinol, memantine and vitamin E for cramps in MND. Other drug treatments may work but have little or no evidence for or against their use. In the absence of any studies relating to physical therapy, such therapies might also be considered as a treatment option.

Treatment for spasticity

It is uncertain whether an endurance-based exercise programme may be useful for the treatment of spasticity as the evidence is of very low quality. In the absence of any RCTs relating to the current practice of a programme of regular stretching, and use of drugs such as baclofen, no statement can be made about efficacy based on any high-quality study.

Mechanical ventilation for supporting respiratory function

Non-invasive ventilation probably has survival and QoL benefit in people with good or moderate bulbar function, and QoL benefit in people with poor bulbar function.

Treatment for sialorrhoea

Botulinum toxin type B injections to parotid and submandibular glands are probably effective in the short term (up to 4 weeks). There is probably no benefit for sialorrhoea beyond this time after a single injection.

Enteral tube feeding for supporting nutrition

There is an absence of any evidence from RCTs for or against the efficacy of percutaneous endoscopic gastrostomy (PEG) insertion for supporting nutrition. Non-randomised and other study design publications provide a rationale for this intervention.

Interventions at the level of activity and participation

Repetitive transcranial magnetic stimulation

It is uncertain whether rTMS improves disability.

Therapeutic exercise

Exercise may improve disability in the short term (3 months).

Multidisciplinary care

There are no RCTs in this area. There is a clinical consensus that multidisciplinary care should be provided where available and this is reflected in the recently updated UK National Clinical Guideline Centre (NICE) recommendations (NICE 2016). The absence of proof that multidisciplinary care is effective must not be interpreted as proof that this approach is ineffective.

Implications for research

This overview has highlighted a significant gap in the current literature. There is need for:

1) appropriate study designs, robust methodology and longitudinal data which address the changing needs-of people with MND and their caregivers-associated with MND disease progression and mortality;

2) studies to assess the:

- effectiveness of interventions on all symptoms relating to MND, including symptoms such as pseudobulbar lability and cognitive and behavioural difficulties;
- benefits of interventions on quality of life (QoL);
- effectiveness of specific interventions (and components), such as:
    - physical therapy for the treatment of cramps;
    - drug treatments and stretching for spasticity;
    - type, intensity, frequency of interventions; and
- the cost effectiveness of interventions;
- impact of interventions on people with MND and their families;
- other factors that affect outcomes (support, adaptive aids and equipment, end-of-life issues);

3) the use of appropriate outcome measures including:

- reliable and valid outcome measures which reflect domains of the International Classification of Functioning, Disability and Health (ICF), are sensitive to what is being measured (such as QoL) and to end-of-life care needs;

4) research into different phases of MND, hence covering the spectrum of care required for this population.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. AMSTAR tool: quality assessment criteria

Criteria	Specific requirements
1. Was an 'a priori' design provided?	The research question and inclusion criteria should be established before the conduct of the review
2. Was there duplicate study selection and data extraction?	There should be at least two independent data extractors and a consensus procedure for disagreements should be in place
3. Was a comprehensive literature search performed?	At least two electronic sources should be searched. The report must include years and databases used (e.g. CENTRAL, Embase, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialised registers, or experts in the particular field of study, and by reviewing the references in the studies found
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language, etc
5. Was a list of studies (included and excluded) provided?	A list of included and excluded studies should be provided.
6. Were the characteristics of the included studies provided?	In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analysed e.g. age, race, sex, relevant socioeconomic data, disease status,

Table 1. AMSTAR tool: quality assessment criteria (*Continued*)

	duration, severity, or other diseases should be reported
7. Was the scientific quality of the included studies assessed and documented?	'A priori' methods of assessment should be provided (e.g. for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	The results of the methodological rigour and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations
9. Were the methods used to combine the findings of studies appropriate?	For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi^2 for homogeneity, I^2). If heterogeneity exists a random-effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?)
10. Was the likelihood of publication bias assessed?	An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available tests) and/or statistical tests (e.g. Egger regression test)
11. Was the conflict of interest stated?	Potential sources of support should be clearly acknowledged in both the systematic review and the included studies
Total Score	

Each criterion judged as 'Yes' (score one point), 'No' (score no point), 'Can't answer' (score no point) or 'Not applicable' (score one point). Total score summed out of a maximum 11 points.

Table 2. Characteristics of excluded reviews

Study	Reason for exclusion
Abdul Wahid 2015	Protocol only Disease-modifying treatments (since published in CENTRAL, Issue 10, 2016 in the Cochrane Library)
Maguire 2014	Protocol only
Young 2014	Protocol only
Pastula 2012	Disease-modifying treatment
Beauverd 2012	Disease-modifying treatment
Yi 2012	Protocol only

Table 2. Characteristics of excluded reviews (*Continued*)

Miller 2012	Disease-modifying treatment
Benatar 2009	Disease-modifying treatment
Bongioanni 2009	Protocol only Not related to treatment
Sathasivam 2007	Protocol only Disease-modifying treatment
Orrell 2007	Disease-modifying treatment
Diana 2006	Protocol only Disease-modifying treatment
Bongioanni 2004	Disease-modifying treatment
Annane 2014	Results for people with MND are not reported separately
Payne 2012	Studies included in this review for people with MND are already covered in the included studies
Lee 2012	Not a systematic review
Good 2014	Studies included in this review for people with MND are already covered in the included studies
Paolo 2015	Not a systematic review

Table 3. Characteristics of included reviews

Author/year	Date assessed as up to date	Interventions	Comparisons	Primary and secondary outcomes	Limitations*
Brettschneider 2013	July 2012	Any drug therapy, given by any route, in any dose, administered to relieve pain in ALS/MND	Not stated but assumed one intervention to another or to placebo or no intervention	Primary outcome (impairment): • Pain relief (after 24 hours) (VAS or any other validated scales) Secondary outcomes: *Impairment* • Pain relief (after 7 days) *Adverse events*	No RCTs found

Table 3. Characteristics of included reviews (*Continued*)

Baldinger 2012	Feb 2011	Any drug therapy (oral, subcutaneous or intravenous) or physical treatment which potentially relieves cramps in ALS/MND	Not stated but assumed one intervention to another or to placebo or no intervention	Primary outcome (*impairment*): • Reduction in subjective global impression of muscle cramp burden measured through VAS Secondary outcomes: *Impairment* • Cramp intensity/number of cramps in 24 hours preceding assessment by VAS • Ratio of participants experiencing cramps to total number of participants (in studies where cramps were assessed as adverse events) *Activity and participation* • QoL *Adverse events*	
Ashworth 2012	July 2011	1) Physical therapy/physiotherapy 2) Modalities (e.g. heat, cold, vibration, electrical stimulation) 3) Non-prescription medications (e.g. vitamins, herbals, diet supplements) 4) Chemical neurolysis (e.g. phenol blocks, botulinum toxin) 5) Surgical intervention (e.g. intrathecal pumps, teno-	Not stated but assumed one intervention to another or to placebo or no intervention	Primary outcome (*impairment*): • Reduction in spasticity at three months as measured by Ashworth (or modified Ashworth) spasticity scale Secondary outcomes: *Impairment* • Reduction in spasticity based on history (e.g. spasm frequency score),	

Table 3. Characteristics of included reviews (*Continued*)

		tomy, dorsal rhizotomy) 6) Alternative therapies (e.g. reflexology, aromatherapy, relaxation techniques)		physical examination (e.g. reflex score) or physiology (e.g. pendulum test) *Activity and participation* • Disability/ activity limitation (e.g. functional independence measure) • QoL *Adverse events* *Cost-effectiveness*	
Radunovic 2013	May 2012	All forms of non-invasive ventilation (NIV) and tracheostomy assisted ventilation	No intervention or best standard care	Primary outcome: • Survival as assessed by pooled hazards ratio using life table/Cox regression methods to combine disparate periods of observation from all studies Secondary outcomes: • Survival at 1 month and 6 months and longer *Activity and participation* • Function - such as ALSFRS • QoL *Adverse events*	
Young 2011	September 2010	1) Any drug treatment administered via any route 2) Injection of botulinum toxin in parotid and/or submandibular glands 3) Radiotherapy to the salivary glands 4) Surgical techniques,	One intervention to another or to placebo or no intervention	Primary outcome (*impairment*): • Subjective improvement in sialorrhoea Secondary outcomes: *Impairment* 1. Reduction in amount of saliva production using	

Table 3. Characteristics of included reviews (*Continued*)

		for example the ligation of parotid and submandibular salivary ducts 5) Other treatments identified in the literature such as complementary therapies		an objective measure such as weight of swabs or amount of tissue used *Activity and participation* 1. QoL *Adverse events*	
Katzberg 2011	September 2009	Placement of percutaneous endoscopic gastrostomy (PEG) or other tube feeding	No feeding tube and continued oral intake	Primary outcome: • Survival time Secondary outcomes: *Impairment* 1. Quantitative index of change in nutritional status (e.g. weight change, change in body mass index, other nutritional markers such as pre-albumin level) *Activity and participation* 1. QoL *Adverse events (safety of PEG)*	No RCTs found
Fang 2013	July 2012	Repetitive transcranial magnetic stimulation (rTMS)	No intervention or sham rTMS or physiotherapy or medications or different methods of applications of rTMS such as high-frequency (> 1 Hz) compared to low frequency (≤ 1 Hz) rTMS	Primary outcome (*activity and participation*): • Disability or limitation in activity as measured by ALSFRS-R (6 months) Secondary outcomes: *Impairment* • Changes to muscle strength as measured by Manual Muscle Testing (1 and 6 months or longer) • Changes to	

Table 3. Characteristics of included reviews (*Continued*)

				fatigue as measured by Fatigue Severity Scale (1 and 6 months or longer) *Activity and participation* • Disability or limitation in activity as measured by ALSFRS-R (12 months) *Adverse events*	
Dal Bello-Haas 2013	July 2012	Progressive resistance or strengthening exercise and endurance or aerobic exercise	No exercise or standard rehabilitation management	Primary outcome (*activity and participation*): • Improvement in functional ability, decrease in disability or reduction in rate of decline as measured by ALSFRS-R or other validated outcome measures (3 months) Secondary outcomes: *Impairment* • Decrease in fatigue • Change in rate of decline of muscle strength • Change in rate of decline of aerobic endurance *Activity and participation* • Improvement in psychological status or QoL *Adverse events* (all at 3 months)	
Ng 2011	July 2011	Multidisciplinary care as defined by any intervention delivered by two or more allied health	Lower level or different type of intervention such as "routinely available	Primary outcomes (*activity and participation*): • Improvement	No RCTs found

Table 3. Characteristics of included reviews (*Continued*)

		disciplines (includes nursing physiotherapy, occupational therapy, speech therapy, etc.), directed by a physician, designed to be patient-centred and aimed at maximising activity and participation	local services" or "minimal intervention" (such as information only), waiting list conditions	in QoL Secondary outcomes: *Impairment* • Improvement in Impairment (e.g. FVC) *Activity and participation* • Improvement in functional ability (e.g. ALSFRS) • Participation and environmental or personal context (e.g. caregiver strain index) *Survival* *Hospitalisation such as readmission and hospital length of stay* *Adverse events* *Cost-effectiveness of care*	

*Not clearly covered by AMSTAR assessment

Abbreviations: ALSFRS: Amyotrophic Lateral Sclerosis Functional Rating Scale; FVC: forced vital capacity; QoL: quality of life; RCT: randomised controlled trial; VAS: visual analogue scale

Table 4. AMSTAR ratings of included reviews

Author/ year	Brettschneider 2013	Baldinger 2012	Ashworth 2012	Radunovic 2013	Young 2011	Katzberg 2011	Fang 2013	Dal Bello-Haas 2013	Ng 2011
'A priori' design for the systematic review provided	Y	Y	Y	Y	Y	Y	Y	Y	Y
Duplicate study selection and data extraction	Y	Y	Y	Y	Y	Y	Y	Y	Y

Table 4. AMSTAR ratings of included reviews (*Continued*)

Comprehensive literature search	Y	Y	Y	Y	Y	Y	Y	Y	Y
Search for studies regardless of their publication type	Y	Y	Y	Y	Y	Y	Y	Y	Y
List of included and excluded studies provided	Y	Y	Y	Y	Y	Y	Y	Y	Y
Characteristics of included studies provided	NA	Y	Y	Y	Y	NA	Y	Y	NA
Scientific quality of included studies assessed and documented	NA	Y	Y	Y	Y	NA	Y	Y	NA
Scientific quality of included studies used appropriately in formulating conclusions	NA	Y	Y	Y	Y	NA	Y	Y	NA
Appropriate methods used to combine study find-	NA	Y	Y	Y	Y	NA	Y	Y	NA

Table 4. AMSTAR ratings of included reviews (*Continued*)

ings									
Likelihood of publication bias assessed	NA	Y	Y	NA	NA	NA	Y	Y	NA
Conflict of interest stated for both the systematic review and included studies	NA	N	N	N	N	NA	N	N	NA
Total score (n/11)	11	10	10	10	10	11	10	10	11

Y = Yes - criteria met (score one point), N= No - criteria not met (score 0 points), CA = Can't answer (score 0 points), NA= not applicable (score 1 point)

Table 5. Overview of reviews

Interventions at the level of impairment/symptoms					
Drug therapy for pain					
Author/year	**Participants**	**Interventions**	**Comparisons**	**Outcomes in the review for which data are available**	**Quality of the evidence (GRADE) for reported efficacy outcomes**
Brettschneider 2013	None	Not applicable	Not applicable	Not applicable	No RCTs found
Treatment for cramps					
Baldinger 2012	13 RCTs N = 4012[1]	Tetrahydrocannabinol (THC), vitamin E, baclofen, riluzole, L-threonine, xaliproden, memantine, gabapentin,	Placebo	Primary outcome: • Memantine, tetrahydrocannabinol (THC) are probably ineffective (moderate-quality evidence) • vitamin E may be ineffective	Very low: L-threonine - 3 studies with very high risk of bias (very small sample sizes, unclear randomisation process and allocation concealment, incom-

Table 5. Overview of reviews (*Continued*)

				• It is uncertain whether L-threonine, gabapentin, xaliproden, riluzole, or baclofen are effective (very low quality evidence, or data not reported) Secondary outcomes: 1. Cramp intensity/number of cramps in 24 hours preceding assessment by VAS - no statistical difference for THC (not assessed in other studies) 2. Ratio of participants experiencing cramps to total number of participants (in studies where cramps were assessed as adverse events) - not an outcome of interest in this review 3. QoL - not measured 4. Adverse events Adverse effects for riluzole 100 mg/day - increased asthenia, spasticity, increase in liver enzymes, impaired respiratory function, and elevation in blood pressure Adverse effects for	plete outcome data) Baclofen - 1 study with high risk of bias and very small sample sizes; subjective impression of cramps listed as an outcome but data not reported Low: Vitamin E - 1 study with clear randomisation, allocation concealment, and blinding, but high risk of selective reporting given change in protocol and no information given on number of participants at 12 months or date of last examination Moderate: THC - 1 study with low risk of bias Memantine - 1 study with low risk of bias Outcome not reported: Riluzole - 3 studies, 2 of which had high risk of bias due to incomplete reporting and 1 at low risk of bias; cramps listed as an outcome but data not reported Xaliproden - 2 studies with low risk of bias; cramps an outcome but results not given Gabapentin - 1 study with low

Table 5. Overview of reviews (*Continued*)

				vitamin E, baclofen, gabapentin, L-threonine, xaliproden, memantine and THC not stated	risk of bias. Cramps an outcome but data not reported
Treatment for spasticity					
Ashworth 2012	1 RCT N = 25	Endurance exercises	"Usual activities"	Primary outcome: Reduction in spasticity in favour of treatment group (mean reduction of −0.43, 95% CI −1.03 to 0.17 in intervention vs increase of 0.25, 95% CI −0.46 to 0.96 in control) Secondary outcomes: No statistically significant differences between exercise and placebo groups in muscle strength (manual muscle testing, fatigue (fatigue severity scale) and QoL (SF-36). No adverse effects reported	Very low: 1 trial with high risk of bias, unclear randomisation, no allocation concealment, no blinding, 50% attrition by 6 months
Mechanical ventilation for supporting respiratory function					
Radunovic 2013	1 RCT N = 41	Non-invasive ventilation (NIV)	"Standard care"	Primary outcome: Median survival was 48 days longer (219 days vs 171 days) compared to the standard care group (estimated 95% CI 12 to 91 days, P = 0.0062). In subgroup analyses, median survival of subgroup with good or moder-	Moderate: 1 trial with low risk of bias (clear random sequence generation, adequate allocation concealment, data was complete and there was no selective reporting or other bias. Blinding of participants was

Table 5. Overview of reviews (*Continued*)

				ately impaired bulbar function was significantly different in favour of NIV group (P = 0.0059) with survival 205 days longer than standard care participants (median 216 in NIV group vs 11 days in standard care group). In participants with poor bulbar function, NIV did not confer survival advantage (P = 0.92) Secondary outcomes: 1) QoL - significant benefit in favour of NIV in *maintenance* of QoL in good or moderately impaired bulbar function subgroup (P = 0.0017 SF-35 Health Survey mental component summary score; P = 0.0013 mean symptoms domain of the sleep apnoea QoL index) and significant benefit in favour of NIV in subgroup of poor bulbar function in *improvement* in mean symptoms domain of the sleep apnoea QoL index but not in the SF-36 Health Survey mental component summary score	not possible and it was unclear if outcome assessors were blinded) Originally 2 RCTs were identified with a total of 54 participants; however, 1 was a pilot study with no study protocol and incomplete data (data available for 6 out of the 13 participants) and was therefore not included in meta-analysis

Table 5. Overview of reviews (*Continued*)

				2) Function - such as ALSFRS - not measured 3) No adverse events reported.	
Treatment for sialorrhoea					
Young 2011	1 RCT N = 20	Botulinum toxin B injection into parotid and submandibular glands	Placebo (normal saline)	Primary outcome: Subjective improvement in sialorrhoea at week 2 and 4 in favour of treatment group (treatment 82% improved, placebo 38%, P < 0.05 at week 2; treatment 90% improved, placebo 44%, P < 0.05 at week 4. No statistically significant difference at week 8 or 12 Secondary outcomes: 1) Volume of saliva produced as measured with funnel and tube over 5 min - significant difference in favour of treatment group at week 2 (treatment 0.07, SD 0.2; placebo 0.84, SD 0.8, P < 0.05) and week 4 (treatment 0.02, SD 0.04; placebo 0.97, SD 0.5, P < 0.05), but not at week 8 or 12 2) QoL as measured by clinicians' assessment of marked improvement using the SEIQOL-	Moderate: 1 trial, small sample size but low risk of bias. By 12 weeks, 70% of investigators and 90% of participants guessed treatment allocation correctly suggesting that despite excellent attempts to maintain blinding, the double-blind was not preserved

Table 5. Overview of reviews (*Continued*)

				DW showed a statistically significant difference from baseline with botulinum toxin but not placebo at week 2 but not at later time points 3) No adverse events reported	
Enteral tube feeding for supporting nutrition					
Katzberg 2011	None	Not applicable	Not applicable	Not applicable	No RCTs found
Interventions at the level of activity and participation					
Repetitive transcranial magnetic stimulation					
Fang 2013	3 RCTs, N = 50	Repetitive transcranial magnetic stimulation (rTMS)	Sham rTMS	Primary outcomes: not measured. Secondary outcomes: No statistical difference in disability or limitation in activity as measured by ALSFRS-R (12 months) or muscle strength Changes to fatigue not measured. No adverse effects reported	Very low: All trials of poor methodological quality (2 of the 3 were missing raw numerical data), insufficiently homogenous to pool results, small sample sizes and high attrition (30% to 40%)
Therapeutic exercise					
Dal Bello-Haas 2013	2 RCTs, N = 43	Exercise (endurance or resistance)	"Usual activities" or "usual care" (stretching exercise)	Primary outcome: Significant improvement in disability or limitation in activity as measured by ALSFRS in favour of exercise groups (3 months) (MD 3.21, 95% CI 0.46 to 5.96) Secondary	Low: Both trials had small sample sizes. 1 trial had a low risk of bias, whilst the other had high attrition (close to 30% by 3 months), no allocation concealment, and no blinding

Table 5. Overview of reviews (*Continued*)

				outcomes: No statistically significant differences between exercise and placebo groups in QoL (SF-36), fatigue (fatigue severity scale) or muscle strength (manual muscle testing) No adverse effects reported	
Multidisciplinary care					
Ng 2011	None	Not applicable	Not applicable	Not applicable	No RCTs found

Abbreviations: ALSFRS: Amyotrophic Lateral Sclerosis Functional Rating Scale; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; CI: confidence interval; MD: mean difference; QoL: quality of life; RCT: randomised controlled trial; SD: standard deviation; SEIQOL-DW: Schedule for Evaluation of Individual Quality of Life-Direct Weighting; SF: Short Form Health Survey; vs: versus.

1. The review includes 20 trials, of which 7 assess cramps as an adverse event. We did not report the trials of cramps assessed as an adverse event in this overview.

APPENDICES

Appendix 1. Cochrane Database of Systematic Reviews search strategy

#1 MeSH descriptor: [Motor Neuron Disease] explode all trees
#2 "motor neuron disease" or "motor neurone disease" or "motoneuron disease" or "motoneurone disease"
#3 "Amyotrophic Lateral Sclerosis"
#4 Gehrig near (disease or syndrome)
#5 (#1 or #2 or #3 or #4)

CONTRIBUTIONS OF AUTHORS

LN prepared the first draft of the protocol and review. FK and CY commented on and edited the first and subsequent drafts. All authors approved the final version.

DECLARATIONS OF INTEREST

LN and FK: no known conflicts of interest. LN, FK and CY were authors on reviews included in this overview.

CY has published and lectured on fatigue in various neurological conditions, including MND, and is very involved in MND research, for which the NHS receives payment. She has had funding from pharmaceutical companies to attend and present at educational meetings. She has received payments for consultancy, teaching or educational presentations from Teva, Merck, Roche, and Genzyme.

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External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Amyotrophic Lateral Sclerosis [*complications]; Enteral Nutrition; Exercise Therapy; Motor Neuron Disease [complications]; Muscle Cramp [*drug therapy; etiology]; Muscle Spasticity [etiology; *therapy]; Noninvasive Ventilation; Pain [*drug therapy; etiology]; Respiratory Insufficiency [etiology; *therapy]; Review Literature as Topic; Sialorrhea [etiology; *therapy]; Transcranial Magnetic Stimulation

MeSH check words

Humans