



The evidence for symptomatic treatments in amyotrophic lateral sclerosis

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Purpose of review

Amyotrophic lateral sclerosis (ALS) is a progressive, incurable and fatal neurodegenerative disease. Few interventions significantly alter the disease course, but many symptomatic treatments exist to improve patients' quality of life. In this review, we describe our approach to symptomatic management of ALS and discuss the underlying evidence base.

Recent findings

Discussion focuses predominantly on recently published articles. We cover management settings, disease-modifying treatment, vitamin D, respiratory management including noninvasive ventilation and diaphragmatic pacing, secretions, nutrition, dysphagia and gastrostomy, communication problems, mobility, spasticity, pain, cognition, depression and emotional lability, fatigue, sleep disturbance, head drop, prevention of deep venous thrombosis and end-of-life issues.

Summary

Multidisciplinary specialist care appears to improve quality of life and survival. Riluzole remains the only available disease-modifying medication and confers a survival advantage of 2–3 months. Noninvasive ventilation improves quality of life and extends survival by approximately 7 months, at least in patients without severe bulbar problems. Nutrition is an independent prognostic factor; whether gastrostomy improves survival and quality of life remains unclear and further studies are underway. Many other symptomatic treatments appear helpful to individuals in clinic, but further randomized clinical trials are required to provide a more robust evidence base.

Keywords

amyotrophic lateral sclerosis, motor neuron disease, symptomatic, treatment

INTRODUCTION

Amyotrophic lateral sclerosis (ALS, motor neuron disease) is a progressive, incurable and fatal neurodegenerative disease. The cause remains incompletely understood, resulting in a lack of effective disease-modifying therapies. In the past, this sometimes led to therapeutic nihilism with patients discharged home to die following diagnosis. This was clearly unacceptable and, although more effective disease-modifying treatments remain urgently required, much can be done to help people living with ALS (Table 1). The symptoms of ALS are many and varied, and a multidisciplinary approach is essential. In this review, we discuss modern management of ALS and the evidence underpinning various interventions.

THE IMPORTANCE OF SETTING

Multidisciplinary care in ALS clinics appears superior to care in general neurology clinics; median survival

was 19 versus 11 months from symptom onset in a recent retrospective review of 417 patients [1[■]], consistent with most [2,3] but not all [4] previous studies. There may also be quality of life benefits [5]. Early access to specialist therapies and better coordination of care are thought to be responsible for the survival difference [1[■]], which are amongst the most significant interventions in the field of ALS care. However, the data are derived from observational studies and a randomized controlled trial (RCT) is required for confirmation [6]. A typical multidisciplinary team includes neurologists, specialist nurse, respiratory physiologist, physiotherapist, occupational therapist, dietician, speech/swallowing therapist, social

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KEY POINTS

- Although ALS remains a progressive and incurable disease, there are multiple interventions that can help alleviate symptoms.
- Management is optimized in a multidisciplinary team setting; observational studies suggest that this improves survival by around 8 months.
- Riluzole is the only medication shown to slow disease progression in amyotrophic lateral sclerosis (ALS); the benefit is modest, on average extending life by 2–3 months in a meta-analysis of randomized controlled trials.
- Timely institution of noninvasive ventilation at the time of respiratory failure improves quality of life and, at least in patients without severe bulbar symptoms, conferred a survival advantage of around 7 months in a single randomized controlled trial.
- Nutrition has been shown to be an independent prognostic indicator. Gastrostomy insertion should be considered when bulbar symptoms advance; it remains unclear whether this intervention improves quality of life and survival and further study is underway.

worker, benefits advisor and gastroenterologist/anaesthetists experienced in gastrostomy insertion in patients with respiratory compromise.

DISEASE-MODIFYING TREATMENT

Riluzole remains the only disease-modifying therapy proven effective in ALS [7,8]. Mean survival benefit from meta-analysis of RCTs is 2–3 months [9]. Riluzole is generally well tolerated; monitoring of full blood count and liver function is required.

POTENTIAL NEW TREATMENTS

Many other disease-modifying agents have been trialled in ALS. Although many appeared promising in preclinical studies, dexamipexole being a recent example [10], unfortunately none have since emerged effective in RCTs [11^{***}]. Pharmacological management of disease progression has not advanced since riluzole was licensed in 1996. There is no evidence to support use of creatine [12] or antioxidants, such as coenzyme Q10 [13] and vitamin E [14]. Recently, vitamin D deficiency has been proposed to contribute to ALS pathogenesis. Eighty-one percent of 37 ALS patients were vitamin D deficient in one study [15^{***}]. A small reduction in decline in ALS functional rating score was reported at 9 months in 20 patients from the cohort who received 2000 international units of vitamin D compared with

Table 1. Summary of symptomatic treatments commonly used in patients with amyotrophic lateral sclerosis

Symptom	Commonly used treatments
Disease progression	Riluzole <i>Vitamin D if deficient</i>
Respiratory failure	Noninvasive ventilation (NIV) <i>Diaphragmatic pacing</i>
Laryngospasm	Reassurance, prn low dose benzodiazepines (e.g. sublingual lorazepam 1mg)
Chest infection	Early antibiotics, chest physiotherapy
Hypersalivation	Hyoscine, salivary gland botox, atropine drops, amitriptyline
Difficulty expectorating secretions	Carbocysteine, breath-stacking, cough-assist machine
Dysphagia and poor nutrition	Soft diet, chin-tuck, supplements, gastrostomy
Communication problems	Speech therapy, lightwriters, Apps <i>Voice banking</i>
Poor mobility	Physiotherapy, mobility aids
Spasticity	Physiotherapy, exercise, baclofen, tizanidine, dantrolene
Pain: Musculoskeletal	Physiotherapy, paracetamol, naproxen, codeine,
Neuropathic	Amitriptyline, gabapentin
Cramps	Baclofen, gabapentin, (quinine – with caution)
Cognitive problems	Neuropsychology, occupational therapy
Depression	Citalopram, venlafaxine, nortriptyline
Emotional lability	Citalopram
Fatigue	Occupational therapy
Head drop	Collars
Prevention of deep venous thrombosis	Compression stockings, dalteparin in inpatients
Care of the dying	Morphine, hyoscine, midazolam

Treatments in italics are recent developments undergoing further research. The evidence base for the various commonly used treatments is discussed in the text.

those who did not [15^{***}]. In a retrospective review of 94 ALS patients, lower vitamin D levels correlated with faster disease progression and shorter survival [16]. Oxidative stress and mitochondrial dysfunction have been mechanistically proposed for these associations [17], but a causal relationship remains unproven and the role of supplementation is unclear; an appropriately powered RCT is required.

RESPIRATORY FAILURE AND NONINVASIVE VENTILATION

Respiratory muscle weakness is common in ALS. Poor sleep, anorexia, malaise and morning headaches

may precede orthopnoea and dyspnoea. The advent of noninvasive ventilation (NIV) has made respiratory failure treatable (Fig. 1). An RCT of 41 patients demonstrated a median survival benefit of 205 days in patients without severe bulbar dysfunction, and improvements in quality of life measures across all patients [18]. Further RCTs are required [19^{***}], as are evidence-based parameters to guide timing of NIV initiation [20]. In the UK, National Institute of Clinical Excellence guidelines recommend regular inquiry about symptoms of respiratory failure in clinic, measurement of forced vital capacity (FVC) and pulse oximetry [21]. If respiratory failure is suspected, we proceed to overnight transdermal assessment of oxygen and carbon dioxide (CO₂) [22] and arterial blood gas analysis [21]. Patients with symptoms and an FVC less than 80%, an FVC less than 50% or in rapid decline even if asymptomatic, or hypercapnia on transdermal CO₂ assessment/arterial *p*CO₂ more than 6 kPa are offered NIV [21,23]. The primary goal of quality of life improvement is often achievable. NIV usage has increased 300% in recent years [24], and initial concerns about overburdening carers appear unfounded [25].

Respiratory specialist teams are invaluable; oxygen humidification or optimizing mask fitting help patients tolerate NIV; multiple nasal and mouth masks are available [23]. Nasal pillows facilitate communication and eating. However, patients with marked cognitive or bulbar problems may still struggle to tolerate NIV [21,24].

In the UK, tracheostomy ventilation is generally avoided. Practice differs elsewhere [26] and some advocate consideration of tracheostomy in young well motivated patients who cannot tolerate NIV [27].



FIGURE 1. Noninvasive ventilation.

DIAPHRAGM PACING

Although beneficial, NIV is not without problems, as the masks can cause issues with claustrophobia, discomfort and act as a barrier to communication. NIV is not tolerated well in many patients with bulbar dysfunction. These issues have driven interest in alternative strategies to support failing respiratory muscles. Diaphragmatic pacing is an exciting new development. The diaphragm muscle is stimulated with surgically implanted electrodes through a pacemaker in the abdominal wall. Some residual diaphragmatic function appears necessary and general anaesthesia is required, which can be risky; careful patient selection appears crucial [28].

In the USA, the technique is available as a funded treatment, but effectiveness is yet to be established in RCTs. An initial pilot study [29^{***}] of 16 patients reported qualitative improvements in diaphragmatic movement, thicker diaphragm muscles and nonsignificant trends towards a slower decline of FVC (−2.38%/month pretreatment and −1.34%/month posttreatment). Another study [30] reported improvements in sleep efficiency measured with polysomnography. In contrast, the authors of another small series of eight ALS patients [31] reported that insufficient tidal volumes could be achieved; no benefits in vital capacity, sleep or survival were found and their patients required NIV. Diaphragmatic pacing is now being systematically evaluated in a number of prospective studies [32].

SECRETION MANAGEMENT

The problem in ALS is twofold; sialorrhoea and difficulty expectorating sputum; these problems commonly coexist.

Data for sialorrhoea management are derived from non-ALS populations and there are few RCTs [33]. Practice varies widely [34]. Subjective benefits from various medications are reported [35]. We use hyoscine patches as first-line. Amitriptyline or atropine drops can be added, but evidence is stronger for salivary gland botulinum toxin (botox) injections [36,37] and we use these as second-line. Benefits typically last several months and treatment can be repeated. In resistant cases, some advocate radiotherapy to the salivary glands [38]; we rarely find this necessary.

Treatment of sialorrhoea can make expectoration even more difficult by increasing respiratory secretion viscosity. Mucolytics, such as carbocysteine, breath-stacking techniques and cough-assist machines [39], which alternate positive and negative pressures (Fig. 2) to improve cough airflow [40]



FIGURE 2. Examples of cough assist machines; the machine on the right is currently used in our clinic.

and perhaps prevent hospitalizations [41], may help. There are no RCT data to support these measures.

DYSPHAGIA, NUTRITION AND GASTROSTOMY

Malnutrition is common [42], an independent prognostic factor [43] and weight loss is associated with poorer quality of life [44[■]]. However, it remains unclear whether optimizing nutrition improves survival or quality of life [45]. We routinely ask about dysphagia (which is usually preceded by dysarthria), monitor weight and refer early to swallowing/language therapists and dietitians. For early dysphagia, softer diet and chin-tuck techniques to avoid aspiration may be recommended. The optimal diet in ALS is unknown; high fat/calorie diets are proposed to be beneficial; an RCT is ongoing (ClinicalTrials.gov NCT00983983).

As ALS progresses, gastrostomy may be considered with the goal of avoiding a hungry patient unable to fulfil their nutritional requirements. Choking, recurrent aspiration, meals becoming an ordeal or significant weight loss (>10%) despite supplements are reasons patients and clinicians may together choose this option. Optimal timing remains unclear; people may decline gastrostomy early in the disease process [46], but once respiratory failure develops, the procedure becomes more risky. In patients with respiratory failure, we prefer per-oral radiologically inserted gastrostomy (PIG), a hybrid approach combining benefits of traditional endoscope-guided (PEG) and radiologically guided (RIG) gastrostomy insertion techniques. Large-bore, robust tubes can be placed

without endoscopy and sedation [47[■]]. No comparative RCTs currently exist. Standard enteral formulas are used, providing 25–30 kcal/kg and 0.8–1.2 g/kg protein/day [48].

Although generally well tolerated [49], it remains unclear whether gastrostomy improves quality of life [50] or survival. Observational studies have suggested benefit [51,52], but no RCTs exist [45]. A large prospective registry of gastrostomy outcomes in ALS patients in the UK has been established in an attempt to develop the evidence base in this area (<http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=9923>).

A recent study suggested that patients with pure upper motor neuron dysphagia may benefit from upper oesophageal sphincter botox injections, which reduced aspiration and delayed gastrostomy in this select group [53[■]].

COMMUNICATION DIFFICULTIES

The traditional approach involves early referral to speech therapists and, as ALS progresses, communication devices may improve quality of life [54]. Lightwriters and inexpensive Apps for tablet computers can be used to generate electronic speech in response to typewritten language. Although adequate hand motor function is required, in patients with severe paralysis, eye-tracking software can be very effective.

Voice banking [55] is a new approach. Although electronically synthesized voices can be distinctive, for example in the case of Stephen Hawking, generally expression, emotional content and accent are lost. Personalized voices can be synthesized by patients preemptively recording their speech; alternatively, relatives can act as ‘voice donors’. Technological innovations, including algorithms requiring minimal voice samples [56], and improvements in automated speech recognition [57], making disordered speech interpretable [56], are advancing the field.

MOBILITY AND SPASTICITY

Mobility needs change over time. Physiotherapists and occupational therapists adapt their approach accordingly through gait analysis, mobility aids, wheelchair assessments and stretching to prevent contractures. Tirasemtiv is a troponin activator proposed to improve muscle power [58[■]]; phase IIb RCT results are awaited (NCT01709149).

Spasticity is common and often associated with painful cramps. One small RCT reported short-term benefits of exercise [59]. Subjective improvements were reported in another small

trial of baclofen [60], but overall evidence is lacking [61]. We involve physiotherapists and sometimes prescribe baclofen or gabapentin, reserving tizanidine and dantrolene for more severe cases. Caution is required, as some patients require spasticity in weak limbs to maintain posture. In nonambulant patients with severe spasticity refractory to medical treatment, intrathecal baclofen pumps have been studied [62]; we use them rarely.

PAIN MANAGEMENT

The cause is poorly understood. Musculoskeletal, neuropathic pain and cramps are all recognized. A phase III RCT of gabapentin assessed muscle cramps as a secondary outcome and found no clear benefit [63]. Recent meta-analyses reported that there is insufficient evidence on which to base recommendations in treatment of either cramps [64] or ALS pain in general [65^{*}]. We involve physiotherapists, treat musculoskeletal pain with paracetamol, non-steroidal anti-inflammatories and opioids, neuropathic pain with gabapentin and amitriptyline, and cramps with baclofen, gabapentin and quinine (the latter with caution due to risk of cardiac arrhythmias).

COGNITION

Cognitive problems are detectable in approximately 50% of patients [66]. Recent genetic advances, such as discovery of the C9orf72 mutation [67,68], have established pathological links between ALS and frontotemporal dementia [69]. Cognitive problems are important, as they confer a worse prognosis [70], make activities of daily living more difficult [71], produce additional burdens for caregivers who may consequently require more support [72] and influence capacity for difficult decision-making. Rapid identification is facilitated by screening tools, such as Edinburgh Cognitive Assessment Scoring [73^{*}]. Treatment is difficult; neuropsychological testing may clarify domains affected and enable occupational therapists to provide practical strategies.

DEPRESSION AND EMOTIONAL LABILITY

Depression is common and psychological support is vital to patients and family members. Standard antidepressants and cognitive-behavioural approaches are used, but no RCTs specific to ALS exist.

We generally treat emotional lability, defined as sudden outbursts of tears or laughter incongruous to circumstance, with citalopram or tricyclic antidepressants. Evidence from RCTs supports the use

of dextromethorphan/quinidine [74,75]; although more experience is required to define long-term safety and efficacy, the combination is well tolerated [76^{**}].

FATIGUE

The complaint of fatigue should prompt consideration of the cause, for example, early respiratory failure or malnutrition, which directs management. Medication side effects, anaemia and other coincidental comorbidities should be excluded.

Treatment data for fatigue are lacking. Exercise was assessed in small trials [59,77]; meta-analysis of results demonstrated some benefits on ALS functional rating scales, but no effect on fatigue or quality of life [78^{*}]. Two small studies, one open-label [79] and one placebo-controlled [80], reported benefits of modafinil, but a meta-analysis concluded that no conclusions could yet be drawn from available data [81]. We involve occupational therapists and generally try to avoid medication if possible, finding efficacy unrewarding and side effects common.

SLEEP

Similar to fatigue, poor sleep should prompt consideration of cause. Fragmented, unrefreshing sleep is an early sign of respiratory failure and responds to NIV. Poor sleep can also be due to depression, pain or difficulty turning in bed because of truncal weakness. Benzodiazepines should generally be avoided especially if respiratory dysfunction is present, and are rarely required.

HEAD-DROP

Head-drop can be disabling. Supportive collars are the mainstay of management. Neck anatomy is highly variable requiring collars to be tailored to individuals; this is being addressed with projects such as 'Head-Up' (<http://www.hsc.nihr.ac.uk/topics/sheffield-support-snood-for-neurodegenerative-cond>).

PREVENTION OF DEEP VEIN THROMBOSIS

Low molecular weight heparin [82,83] and compression stockings [84] reduce deep vein thrombosis (DVT) incidence in hospital inpatients overall, and all-cause mortality was also lower in one study [85]. However, thromboprophylaxis may not necessarily be suitable for all, for example, compression stockings appear detrimental in stroke patients [86] and existing data may not necessarily apply to older

patients [87]. No mortality data or treatment RCTs exist in ALS.

A prospective study [88^{***}] of 50 ALS outpatients estimated DVT incidence at 11%/year, increasing to 36%/year in patients with significant leg weakness. We routinely prescribe prophylactic dose low molecular weight heparin to ALS inpatients in the absence of contraindications. We do not currently routinely treat ALS outpatients with thromboprophylaxis and await a RCT.

END-OF-LIFE ISSUES

ALS is ultimately fatal and there comes a time when emphasis shifts to management of death. The right time to breach this subject depends on the individual. Most patients with ALS die from respiratory failure. Patients using NIV may opt to gradually reduce ventilation settings and withdraw treatment; they can be reassured that death is usually peaceful. Standard palliative care measures, such as adequate control of pain, secretions and anxiety are important [89]. Opioids can help alleviate dyspnoea [90]; patients generally prefer inhaled/sublingual administration routes [91]. The needs of carers should not be overlooked [92].

CONCLUSION

ALS remains an incurable, fatal condition and better disease-modifying treatments are urgently required. However, much can be done for people living with ALS while we wait. Symptomatic treatments can improve quality of life, which is paramount when quantity of life is limited. There is good evidence underpinning riluzole and NIV and reasonable evidence for multidisciplinary care. In clinic, many other measures appear helpful to individuals, but evidence is generally weak and RCTs are required. Areas of priority include vitamin D supplementation, role of gastrostomy, optimal management of secretions, pain, spasticity and depression, and DVT prophylaxis. Exciting new techniques such as diaphragmatic pacing are undergoing further evaluation.

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Conflicts of interest

We are involved in ALS research including the DiPALS trial, PROGAS registry and Head-Up project.

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