Article:
Hobson, E.V. and McDermott, C.J. (2016) Supportive and symptomatic management of amyotrophic lateral sclerosis. Nature Reviews Neurology, 12 (9). pp. 526-538. ISSN: 1759-4758

https://doi.org/10.1038/nrneurol.2016.111

Supportive and symptomatic management of amyotrophic lateral sclerosis

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Acknowledgements
This was an invited review. EH and CM were both involved in researching the evidence and writing the article.

Word count: 4476

Conflict of interest statements.
Both EH and CM are investigators in various clinical trials of interventions in amyotrophic lateral sclerosis including diaphragmatic pacing, Sheffield Support Snood, cough augmentation, oropharyngeal secretion management, remote monitoring of non-invasive ventilation and telehealth as well as pharmaceutical studies including the evaluation of tirasemtiv and levosimendan. EH is funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship. CM receives funding from the NIHR, the Motor Neurone Disease Association and EU Joint Programme – Neurodegenerative Disease Research (JPND). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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Abstract

Amyotrophic lateral sclerosis (ALS) is an incurable and terminal disease which causes progressive symptoms that negatively impact on quality of life. The aim of ALS care is to minimise morbidity and maximise quality of life. This review describes the current approaches to supportive care and outlines the evidence for these strategies.

Recent changes
Supportive care for patients with ALS by a specialist multidisciplinary team is associated with improved survival. Respiratory support using non-invasive ventilation can improve survival and sustain quality of life, however the role of diaphragmatic pacing is less clear with several studies reporting reduced survival with its use. There is building evidence of the key role of metabolic dysfunction in the pathogenesis of ALS and that interventions that optimise nutrition may improve quality of life and survival. Cognitive changes are now recognised to occur commonly in ALS and impact on prognosis. How best to intervene and support patients and carers when cognitive changes occur is yet to be established. There is increasing recognition of the need for specialist palliative care to provide support for those facing complex and distressing problems throughout the disease course as well as for those approaching the end of life.

Future research
The basis of supportive management is moving from guidelines based on expert consensus towards an evidence-based approach. This will encourage the use of effective treatments and could reduce the risk of harm caused by ineffective or unsafe interventions.

Key points

- The aim of the management of ALS is to maximise quality of life and minimise morbidity.
- Guidelines for symptomatic care are becoming more evidenced-based.
- Management by specialist clinic based multidisciplinary team is associated with improved survival.
- Non-invasive ventilation improves survival and quality of life in patients with respiratory failure.
- Nutrition is an independent indicator of survival and early insertion of a gastrostomy is recommended prior to significant weight loss.
- Cognitive impairment is common in ALS and is associated with a worse prognosis; optimal management of this problem is unclear.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive, incurable disease causing muscle weakness and paralysis. Whilst the lifetime incidence of ALS is 1 in 400, average survival is only two to four years from onset, meaning prevalence is low (approximately 5.4 per 100 000) [1,2]. The extensive search for a disease modifying therapy has been unrewarding, with riluzole being the only drug shown to offer a small survival benefit of approximately three months [3,4].

There is an increasing recognition of the impact symptoms of ALS have on patients and their families. As a result, the focus of ALS management has shifted towards specialist multidisciplinary care which provides holistic support aiming to minimise morbidity and maximise function and quality of life [5-10]. In the last two decades, major guidelines focussing on supportive care have been developed [11-14]. However, in the absence of evidence, recommendations have largely been based on consensus or expert opinion and individual clinicians' practise varied. This review will discuss the evidence underpinning the approach to supportive care in ALS and priorities for future research. (Table 1)

Organisation of care

The management of patients with ALS care is often led by a multidisciplinary team of specialists working together to provide a rapid and sensitive diagnosis followed by holistic care throughout the disease (Box 1). Attendance at a multidisciplinary clinic is associated with improved survival, independent of the use of non-invasive ventilation, riluzole and gastrostomy feeding [5,10,15,16]. The cause of this additional survival benefit is unknown and is worthy of further study, particularly as it appears that the structure in which care is delivered impacts on patient survival. This was demonstrated in a study comparing models of care in Ireland and Northern Ireland. Centralised multidisciplinary hospital clinic based care was associated with superior outcomes compared to either attending a general neurology clinic with no integrated care or receiving co-ordinated care through a community care network [10]. The reasons behind these differences are unclear, but the survival benefits may relate, in part, to the complex decision-making processes that can take place within the team in the

centralised clinic setting [10].

Attendance at a multidisciplinary clinic may reduce and shorten hospital admissions and patients are more likely to use riluzole, assistive aids and non-invasive ventilation but the impact on quality of life is less clear [6,7,10,17]. Patients value the convenience and quality of unified care but whilst single appointments reduce travel time to multiple specialists, travelling to hospital and the prolonged nature of appointments remains a problem [8,18]. Alternative services such as using telemedicine or remote monitoring may be useful to sustain access to specialists throughout the disease without the need to travel [19]. It will however, be essential to ensure that the beneficial aspects of traditional clinic based multidisciplinary care are incorporated into these new models of service.

Box 1: The components of a multidisciplinary team. The core team members listed have been compiled from those listed in studies evaluating multidisciplinary care in ALS [5-10].

Components of a multidisciplinary ALS team:
Neurologist /rehabilitation physician
Nurse / care coordinator
Physiotherapy
Occupational therapy
Respiratory specialist
Speech therapy
Dietician
Charity worker
Social worker / benefits advisor
Neuropsychology / Psychiatry
Other specialists that may be required:
Gastrostomy services
Palliative care / hospice services
Assistive technology
Wheelchair services
Augmentative and Alternative Communication services
Continence team
In liaison with:
General practitioner
Community "outreach team"
Hospice / hospital at home service

Management of respiratory function

Type two respiratory failure is the most common cause of death in ALS and non-invasive ventilation was the first intervention shown to have a positive impact on both survival and quality of life [20]. Symptoms of respiratory failure can develop insidiously and initially respiratory failure may only occur in REM sleep, when diaphragmatic weakness causes hypoxia and hypercapnoea resulting in sleep disturbance (Table 2). Later in the disease, patients develop dyspnoea at rest, poor cough and respiratory tract infections. These problems are exacerbated by bulbar dysfunction. Early trials of drugs that may improve respiratory muscle contractile force and cough effectiveness are underway [21,22].

Monitoring of respiratory failure

The best strategy for monitoring and identifying respiratory failure is unclear. Expert guidelines recommend regular monitoring of respiratory function at least every three months, by enquiring about symptoms of respiratory failure and using objective measures [11,13,14]. Despite this guidance, in some clinics access to objective measures of respiratory muscle strength is limited and these measurements may be insensitive to respiratory failure and unsuitable for patients with bulbar or cognitive dysfunction [23]. The most basic objective measure advised is daytime oxygen saturations plus either forced vital capacity or sniff-nasal-inspiratory pressure (Box 2). If a patient exhibits signs or symptoms of respiratory failure it is recommended that they undergo arterial or capillary blood gas analysis. It should be noted that oxygen desaturation usually occurs late in type II respiratory failure and daytime measurements of arterial carbon dioxide may not be a reflection of overnight function [20]. Therefore if respiratory failure is suspected and daytime gas analysis is normal then nocturnal oximetry studies should be conducted [14,24]. Non-invasive transcutaneous measurement of carbon dioxide levels is now possible and this can supplement the information from overnight oximetry [25].

Box 2: The objective indicators of respiratory failure.

Objective indicators of respiratory failure
Forced vital capacity < 50%
Forced vital capacity < 80% + symptoms of respiratory failure
SNIP or MIP < 40 cmH2O
SNIP or MIP < 65 cmH2O (men) or 55 cmH2O (women) + symptoms of respiratory failure
Repeated tests show a rate of decrease of SNIP or MIP >10 cmH2O per 3 months
Daytime arterial CO2 of<6kPa with symptoms of respiratory failure
Daytime arterial CO2 of ≥6kPa
Daytime O2 saturations of ≤94%
Nocturnal episodes of hypercapnoea
Nocturnal episodes of hypoxia

SNIP: sniff nasal inspiratory pressure, MIP: mouth inspiratory pressure
Adapted from *The use of non-invasive ventilation in the management of motor neurone disease*, National Institute for Clinical Excellence guidelines. NICE clinical guideline 105 (2010) [14].

Non-invasive ventilation

A randomised controlled trial of patients with ALS using non-invasive ventilation (NIV) demonstrated survival and quality of life benefits [20]. (Figure 1) Using NIV initially at night and also if required, in the daytime, was associated with a median survival gain of seven months and quality of life was improved and sustained throughout the trial.

Using NIV can be challenging, requiring perseverance by patients and carers as well as significant support from specialists [26,27]. Unsurprisingly those with poor adherence or poor ventilation fail to gain survival benefit [28]. Patients in the original trial with poor bulbar function failed to experience a survival benefit but did experience improvement in quality of life [20]. Current guidance recommends that a trial of NIV should be offered to patients even if they may not be able to tolerate NIV because they may experience an improvement in sleep-related symptoms [14]. This approach is supported by a recently published cohort study of 292 patients that suggested that patients with bulbar onset disease may, in fact, gain survival benefit from using NIV [29].

Additional equipment such as humidification and alternative masks may promote adherence by dealing with problems such as dry mouth, claustrophobia and difficulties eating. Battery packs and back-up ventilators reduce the burden on routine life and allow patients to travel [30]. Face-to-face training can be supplemented by online resources such as "MyNIV" (www.mymnd.org.uk), which promotes the benefits of NIV use and encourages adherence [31].

Invasive ventilation

The number of patients undergoing tracheostomy ventilation is increasing but varies from country to country [32,33]. Patients may commence invasive ventilation in a desire to prolong life, when they are unable to tolerate NIV, to manage respiratory secretions or in an emergency following a respiratory crisis [33]. One cohort study did suggest however, that invasive ventilation offers no survival advantage for patients aged over 60 years [32]. Invasive ventilation is limited by

resources and concerns that the patient and carer quality of life may be poor or that patients may become "locked-in", losing the ability to communicate [34]. It is good practice to discuss respiratory failure, potential treatments and end-of-life options early and throughout the disease so that individual wishes are known should an unpredicted respiratory emergency occur [14].

Respiratory and oropharyngeal secretions

Dysphagia and poor cough cause excessive oropharyngeal and respiratory secretions, occurring in approximately half of patients attending ALS clinics [35]. Excessive secretions cause social embarrassment, increase the risk of aspiration and pneumonia, and can impair the use of NIV. Management varies and drug treatments are often ineffective, with half of those experiencing the problem having uncontrolled symptoms [35]. The treatment of thin saliva can dry the mouth and thicken secretions, making their clearance more difficult. Intraglandular botulinum toxin was effective in reducing secretions in a randomised controlled trial of 20 patients and may reduce aspiration [36]. Botulinum toxin is well tolerated and its effectiveness may be improved by using ultrasound-guidance [36-38]. It can cause drying of the mouth and can (rarely) worsen dysphagia and therefore it tends to be reserved for those with a gastrostomy [35,37,39]. Radiotherapy is effective but is limited by availability and risk of permanent dry mouth [40,41]. There are no studies examining the drug treatment of respiratory secretions but mucolytics such as carbocysteine and airway humidification using NIV or nebulised saline are recommended [13,14].

Cough augmentation

Dysphagia and respiratory muscle weakness leads to weakened cough and poor secretion clearance, increasing the risk of respiratory infections. Monitoring cough effectiveness using measures such as peak cough flow may identify patients at risk of ineffective sputum clearance [42,43]. Improving lung recruitment and thereby increasing peak cough flow and sputum clearance may be achieved by using NIV, breathing exercises (e.g. "breath-stacking") or a lung volume recruitment bag [44,45] (Figure 3). Mechanical insufflation-exsufflation devices (e.g. Cough Assist) are more effective in increasing peak cough flow but are difficult to use in those with poor bulbar function [45]. External high frequency chest wall oscillation using a wearable vest may also improve sputum clearance [46]. Cough assist use is recommended during acute infective episodes but trials to determine the benefits of regular prophylactic use of cough augmentation devices are awaited.

Diaphragmatic pacing

In 2011, the United States Food and Drug Administration gave approval for use of a diaphragmatic pacing device in patients with ALS under the Humanitarian Device Exemption program [47]. The approval was based on partially published data from a non-randomised uncontrolled cohort of 86 patients with ALS, which reported a positive impact of diaphragmatic pacing on survival and sleep quality. However, in 2014, a randomised controlled trial of diaphragmatic pacing in the UK found patients using pacing survived on average, 11 months less than who did not undergo pacing [48]. A French study was also terminated early following findings of excess mortality in those who underwent pacing [49]. A US study has

suspended recruitment whilst the implications of the conflicting results are explored, and a post marketing approval registry study continues [50,51]. It may be possible to pool the data from these trials to determine whether there is a role for pacing in a particular sub-group of patients, however for the majority this would appear not to be the case. At present it is recommended that diaphragm pacing is only used within the context of clinical trials [48].

Nutrition and swallowing

Malnutrition and weight loss are well recognised poor prognostic factors in ALS [52-55]. Reasons for weight loss are multifactorial and include muscle wasting secondary to denervation, poor oral intake due to dysphagia, upper-limb weakness and poor appetite and energy intake is lower than predicted daily requirements [56]. Calorie ingestion of less than the recommended daily amount has been observed in 70% and 94% of patients with ALS in two cohorts [57,58]. Low oral intake is compounded by an increased resting energy expenditure which occurs in up to 67% of patients with ALS [52,56,59-61]. The cause of hypermetabolism in ALS is unknown, with several unproven hypotheses including mitochondrial dysfunction [62].

Given the high prevalence of hypermetabolism and the association of weight loss and malnutrition with a poor prognosis in ALS, a small pilot study of high calorie diets in gastrostomy fed patients with advanced disease has been undertaken [63]. The results indicated a possible survival advantage with good tolerability of high calorie supplementation. This demonstrated the potential of a high calorie nutritional intervention to influence the disease course in ALS. Whilst the approach in this study has the advantage of controlling the nutritional intake accurately through a gastrostomy tube, the main draw back is that patients are receiving the nutritional intervention late on in the disease course.

It is recommended that patients undergo regular assessment of swallow and weight, and receive advice regarding diet and swallowing techniques [13]. Exercises to improve cough and swallow and even insertion of autologous myoblasts into the tongue are being explored [64-66]. An observational study injecting botulinum toxin into the upper oesophageal sphincter in 20 patients reduced signs of aspiration but further trials are awaited [67].

Gastrostomy feeding

Enteral feeding is commonly used to sustain intake of nutrition and medication but there is no convincing evidence that it improves survival, nutritional outcomes or quality of life [68]. Given it is already extensively used in ALS, it is unlikely that a randomised controlled trial with a placebo arm to definitively explore this issue would be possible. However, evidence regarding the timing and method of gastrostomy have become clearer following a prospective cohort study of 345 patients undergoing gastrostomy insertion [69]. Whilst expert consensus previously recommended that a loss of 10% of body weight should trigger insertion, this cohort study suggested that this may be too late [11]. Those patients undergoing the procedure who had already lost more than 5% of their premorbid weight were unlikely to regain this weight with enteral feeding [69]. It

is therefore recommended that patients should be referred to a dietician and speech therapist at the onset of dysphagia and consider gastrostomy insertion early in the disease, ideally prior to the development of respiratory failure or significant weight loss [13,69].

Identifying the correct time for an individual to undergo the procedure is challenging and patients often chose to delay insertion, particularly those still enjoying the taste and the social importance of eating [70,71]. Patients may view gastrostomy negatively, as it represents an important milestone in their disease and using a gastrostomy also places a major burden on carers [70,72]. For some patients with severe cognitive impairment or who are frail or nearing the end of life, conservative management may be more appropriate. Alternatives such as nasogastric feeding, subcutaneous fluids or even parental nutrition may be considered [13].

The technique for gastrostomy insertion depends on a patient's respiratory function and available expertise. Endoscopic placement of a percutaneous gastrostomy (PEG) is appropriate for patients without respiratory failure who can tolerate sedation. For those with respiratory failure, radiological guided gastrostomy (RIG) avoids the need for sedation but the balloon-retained tubes are significantly more likely to become displaced, leak or require replacement [70]. Per-oral image-guided gastrostomy (PIG) can be performed whilst using non-invasive ventilation. This involves inserting a nasogastric tube as a guide allowing a robust PEG gastrostomy tube to be pulled through and out of the abdominal wall [70]. All three methods appear to be as safe as each other [69]. Patients may develop bloating or bowel disturbance following initiation of enteral feeding. Adjustment in feed regime may be helpful but there is no evidence to support any specific approach.

Musculoskeletal symptoms

Spasticity

Spasticity causes pain and loss of function and can be exacerbated by factors such as infection and poor positioning. There is no evidence to recommend one management strategy over another [73]. Muscle relaxants can exacerbate muscle weakness and their sedating side-effects are often intolerable. One randomised controlled trial of prescribed exercise in 25 patients observed small improvements in disability and spasticity [74]. In observational studies, intrathecal baclofen improved symptoms and quality of life in patients where oral medication has failed [75,76].

Cramps

Cramps are common in ALS but Cochrane review of trials of various treatments including one randomised controlled trial of tetrahydrocannabinol, reported no evidence to recommend any particular treatment [77,78]. An open label study of levetirecetam in 20 patients has reported a reduction in cramp frequency and severity [79]. Quinine is the most commonly used therapy for cramps but use for

this indication is restricted in the United States because of reports of rare but serious haematological and cardiac events (665 serious events and 93 deaths between 1969 and 2006) [80]. A Cochrane review of quinine in patients with various causes of cramp found moderate evidence that quinine was safe and effective [81]. The side effects of quinine are dose dependent and it is possible that low dose quinine used in cramps may not be associated with these side-effects but the studies included in the review may be too small to detect very rare events [81]. In the absence of an effective alternative, guidance from the American Academy of Neurology recommends that quinine only be used as a last resort [11].

Pain

More than half of those with ALS experience pain and it impacts on quality of life, and a small number experience other sensory symptoms but no trials in ALS have been conducted [82,83].

Psychological symptoms

The incidence of depression ranges from 11% (interview studies) to 75% (self-reported measures) and is associated with a poorer quality of life. There have been no trials of specific ALS treatments, so standard therapies (selective-serotonin reuptake inhibitors, amitriptyline or mirtazapine) are recommended [13].

There is increasing recognition of the overlap between ALS and other neurodegenerative diseases, in particular, frontotemporal dementia and Parkinsonism; both in the same patient, or within their family. Some of these patients have pathogenic mutations, the most common being the recently identified abnormally-long hexonucleotide repeat expansion C9ORF72 [84-86]. Approximately 10-15% of ALS patients will show signs of frontotemporal dementia; typically frontal variant with executive dysfunction, language or behaviour change [87]. A further 50% experience mild cognitive or behavioural change. Patients with executive dysfunction have a poorer prognosis, whilst behavioural change has a negative impact on carer quality of life [87,88]. An ALS specific tool (the Edinburgh Cognitive Behavioural ALS Screen tool) has been developed which can identify frontotemporal deficits [89]. Whilst treatment is not available, early recognition allows the provision of support and coping strategies for patients and carers, and facilitates decision making and advanced planning.

Approximately half of patients experience emotional lability, pathological laughter or crying and this is more common in those with bulbar onset ALS [90]. A selective-serotonin reuptake inhibitor (fluvoxamine) and amitriptyline have been associated with reduced emotional outbursts in small observational studies [91,92]. More recently, two randomised controlled trials of Nuedexta (a combination of dextromethorphan and quinidine) including 333 patients with ALS found a significant reduction in emotional events [93,94]. Side effects include dizziness and somnolence, which led to 24% of patients to stop taking the drug in one study. Nuedexta should be avoided in those with a risk of cardiac arrhythmia as it can prolong the QT interval. It is licensed for use in the United States and is awaiting European license.

Insomnia and fatigue are common and impact on quality of life [95,96]. In one small study modafinil was found to improve symptoms of fatigue but larger studies are required [97]. There have been no studies of interventions for insomnia and therefore standard treatments (hypnotics, mirtazapine and amitritypline) are recommended [13].

"ALS-plus" symptoms

Other neurological disorders including aphasia, ataxia and autonomic dysfunction have also been observed in 14% of patients in one cohort and these patients had a poor prognosis [98]. Given the only recent recognition of these features, there are currently no recommended approaches to management in patients with ALS.

Assistive devices

Assistive devices can improve function and independence but need to be accessible, affordable and appropriate for the changing needs of patients. By working directly with patients and clinicians, specifications for devices to meet the needs of patients with ALS can be established. Two recent solutions have demonstrated the benefit of these collaborations: the Sheffield Support Snood and Powered Neuro Wheelchairs [99,100].

Neck weakness causes head drop; which leads to pain and can exacerbate problems with communication, eating and drooling. Current neck collars were described as being too rigid and restricting movement, or too soft; providing ineffective support [99]. The Sheffield Support Snood was developed in a collaboration involving clinicians, patients and engineers. It offers an adaptable structure which can provide tailored support to an individual that is modified as needs change. (Picture 4) Early evaluation suggests it provides good support without restricting movement, eating or speaking and for most patients was preferable to their previous collar [101].

Using a powered wheelchair improves mobility, independence and quality of life but there is a lack of evidence to determine the appropriate specification for patients with ALS [102,103]. Selection of the appropriate chair relies on the expertise of the therapist and choice may be limited by cost and availability. A collaboration of patients and therapist in the UK, working with wheelchair manufacturers developed three "Powered Neurochairs" [100]. Each offers high specification at an optimum, affordable cost so patients can quickly access a wheelchair that will meet their needs.

Communication

For patients with dysarthria there are many augmentative assistive communication solutions available. These include simple writing boards, text-to-speech apps and eye-gaze systems. Voice banking is a relatively new option that can provide a more natural voice to patients who use text-to-speech apps such as

"Predictable" [104]. Patients can use software such as Model Talker to record their own voice although the quality of the synthesised voice relies on patients recording 1600 phrases, which is time consuming [105]. Patients can adopt a "donated" voice and voice banks are now able to combine multiple voices to provide an individual voice matched to age, sex and accent. There is some way to go before communication devices are fast enough to maintain a conversation and produce a voice that can match the prosody of natural speech [106]. In the future brain-computer interfaces may allow patients with severe disability to communicate using electroencephalogram (EEG) control. Currently this technology has been evaluated in only a small number of patients, mostly in experimental environments and is limited by the usability and reliability of the technology [107].

Care at the end of life

The experience at the end of life can have a significant impact on patients and their families [108-110]. Due to the complexities of management of advanced ALS it is recommended that specialist palliative care services are involved early and throughout the disease [111]. Advanced care planning allows patients and their families to document their attitudes towards future events but enactment of these wishes may not always be straightforward and decisions should be reviewed regularly [112]. Anticipatory prescribing of medications to treat symptoms at the end of life may enable informal carers to administer medication whilst subcutaneous infusions may be required for on-going symptoms (Table 3). The Motor Neurone Disease Association has developed a "Just-in-case" box in which medication for carers or clinicians (e.g. ambulance service or nurses) to use to treat terminal symptoms can be stored and recorded [113].

Withdrawal of ventilation

With progression of respiratory muscle weakness, it is common for individuals to begin to use NIV during the day for symptom relief. At the end of life, some patients die peacefully with NIV in-situ whilst others simply stop using it without experiencing significant difficulties [109]. In a proportion of patients the decision to no longer continue using NIV is more complex. Patients may require the assistance of others, for example, to remove the mask, and may require treatment to prevent distressing symptoms. This can cause anxiety on legal and ethical grounds which may interfere with the delivery of the best end-of-life care [111,114]. The law in many countries recognises that a patient with capacity can opt to refuse or withdraw from medical treatment even if it will result in death.

Guidelines have been drawn up to advise those considering ventilation withdrawal [111,114]. It is recommended that patients, family and clinicians openly discuss their thoughts about ventilation and the circumstances at the end-of-life. These discussions should begin before ventilation commences and continue throughout the illness and may be triggered by situations such as when patients begin to use ventilation in the day to relieve dyspnoea or if topics such as advanced decision-making or euthanasia are raised. If a patient expresses a wish to withdraw from ventilation the patient's capacity must be assessed and it must be established that the decision is the settled position of the individual.

Conscious sedation (i.e. drowsy but awake) using opiates and benzodiazepines should be achieved prior to ventilation withdrawal to avoid distressing symptoms. Deep unconscious sedation may be needed to tolerate withdrawal in those who become breathless quickly after mask removal. Although patients may die quickly, preparations must be made to support patients where the process may take longer [114].

Future research and the need to develop the evidence base for symptomatic care

Given the clear evidence of benefit of non-invasive ventilation, other interventions to managed the consequences of respiratory failure may also improve survival and quality of life. The most important question is whether cough augmentation can reduce the incidence of respiratory infection. Other areas of uncertainty include how to monitor respiratory function, how to improve the tolerance and effectiveness of NIV and the management of oropharyngeal secretions. Focus is also needed to determine the optimum approach to nutrition, pre- and post- gastrostomy and to improve other distressing symptoms that have an impact on quality of life. It will also be important to develop an understanding of the key aspects of multidisciplinary care that improve survival and how these benefits can be delivered to all patients. Like many of the other interventions described in this review, multidisciplinary care has multiple components, each of which may influence the outcome of the intervention. Establishing the aspects of the intervention that are key to its success, in whom they are successful and how they can be delivered will be challenging [115].

Previous guidelines have provided an excellent benchmark for standards of ALS care but in lieu of much high quality evidence, these standards have understandably been largely based on expert and consensus opinion. Developing an evidence base for symptomatic case is important because, whilst improvements have been made over the last decade, access to standard treatments that have been proven to be beneficial remains variable. For example, despite clear evidence to support the use of riluzole, patients attending a non-specialist clinic remain less likely to be receive the drug [10]. Prior to the randomised controlled trial of NIV few patients in the UK were using it [116]. Following this trial and subsequent publication of National Insitute for Clinical Excellence (NICE) guidelines in 2010 in the UK, NIV use has markedly increased [23]. Specialist clinics will promote the use of NIV, but in some areas there still remains a lack of access to monitoring and treatment as well as inequalities in use in some patient groups [23].

Promoting evidence-based guidelines should reduce the potential for patients who feel they have little to lose to be harmed by using unsafe, untested treatments. For example, prior to the recent research demonstrating its potential harm when used in a non-selective manner, diaphragmatic pacing systems were already being widely implanted around the world. This story has several lessons for the ALS community. The most important is that all interventions should be

evaluated thoroughly and usually this will be in the context of a randomised controlled study. The arguments that patients with ALS have nothing to lose and that they have a right to try untested therapies are understandable, given the poor prognosis and the lack of curative treatments [117,118]. However, such approaches can lead to patient harm and become a barrier to the development and evaluation of effective therapies.

Conclusion

Current evidence indicates that supportive care for patients with ALS is best delivered by a specialist multidisciplinary team, which can provide holistic care to patients, family and carers maximising function and quality of life. Further work is needed to strengthen the evidence base for the management of ALS, which ultimately should ensure universal good practice and reduce inequalities in care.

Figure 1: A non-invasive ventilation mask (copyright Sheffield Institute for Translational Neurosciences)
Figure 2: An online guide for people with ALS using non-invasive ventilation. www.mymnd.org.uk (copyright Sheffield Institute for Translational Neurosciences)
Figure 3: A lung recruitment "breath-stacking" device (copyright Sheffield Institute for Translational Neurosciences
Figure 4: The Sheffield Support Snood (copyright Sheffield Institute for Translational Neurosciences)

Table 1: The management of common symptoms in ALS.

Table 2: The symptoms and signs of respiratory failure.

Table 3: The management of symptoms at the end of life.

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Table 1: The management of common symptoms in ALS

Problem	Pharmacological treatments	Grade of recomm-endation	Non-pharmacological strategies	Grade of recomm-endation
Respiratory failure			Non-invasive ventilation [20] Cough augmentation	Grade A Grade D
Excessive respiratory secretions (thick)	Carbocysteine Nebulised saline	Grade D Grade D	Cough augmentation Humidification of NIV Suction Reduction in dairy product intake	Grade D Grade D Grade D None
Excessive oral secretions (thin)	Hyoscine patches Amitriptyline Atropine drops Glycopyrrolate Botulinum toxin [36]	Grade D Grade D Grade D None Grade B	Radiotherapy [40, 41] Pineapple juice Suction	Grade C None Grade D
Dry mouth	Artificial saliva sprays/tablets Saliva stimulating tablets	None None	Humidification of NIV	None
Cramps	Quinine [77, 81] Levetiracetam [79]	Grade B Grade C	Physical therapy/exercise	Grade D
Spasticity	Baclofen/ tizanidine / dantrolene Benzodiazepines Intrathecal baclofen [75, 76]	Grade D Grade D Grade C	Prescribed exercise [74] Hydrotherapy Cryotherapy	Grade B Grade D Grade D
Emotional lability	SSRIs [91] Dextromethorphan / quinidine [93, 94] Amitriptyline [92]	Grade C Grade A Grade C		
Depression	SSRIs	Grade D		
Anxiety	Benzodiazepines	Grade D		
Fatigue	Modafinil [97]	Grade B		

SSRIs: selective serotonin re-uptake inhibitors, DM: dextromethoprhane, Q: quinidine, NIV: non-invasive ventilation
Grading of recommendation proposed by the Oxford Centre for Evidenced-based Medicine, 2009
www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
Grade A: systematic review or individual RCT with narrow confidence interval.
Grade B includes systematic reviews or cohort or case-control studies or extrapolations* of level A studies
Grade C: case-series or poor quality cohort studies or extrapolations* of level A or B evidence
Grade D: expert opinion or inconsistent research from level A, B or C evidence
*extrapolations are where data is used in a situation that has potentially clinically important differences from the original study situation

Table 2: The symptoms and signs of respiratory failure.

Symptoms of respiratory failure	**Signs of respiratory failure**
Breathlessness	Increased respiratory rate
Orthopnoea	Shallow breathing
Recurrent chest infections	Weak cough
Disturbed / un-refreshing sleep	Weak sniff
Nightmares	Abdominal paradox (inward movement of the abdomen during inspiration)
Daytime sleepiness	
Poor concentration	Use of accessory muscles of respiration
Poor memory/confusion	Reduced chest expansion on maximal inspiration
Hallucinations	
Morning headaches	
Fatigue	
Poor appetite	
Cough	
Excessive respiratory secretions	

Adapted from *The use of non-invasive ventilation in the management of motor neurone disease*, National Institute for Clinical Excellence guidelines. NICE clinical guideline 105 (2010)[14].

Table 3: The management of symptoms at the end-of-life.

Terminal symptoms	Potential options	Potential first line treatments	Additions & alternatives
Dyspnoea	Opiates Benzodiazepines	Morphine 5-10mg po/PEG/sc Diamorphine 2.5mg s/c	Fans / cool compresses Non-invasive ventilation
Laryngospasm / choking	Benzodiazepines	Lorazepam 0.5mg po/PEG Midazolam 2.5mg s/c	Non-invasive ventilation Suction
Respiratory secretions	Hyoscine butylbromide Glycopyrronium	Hyoscine butylbromide 20mg s/c	Cough-augmentation devices Suction
Terminal agitation	Benzodiazepines	Lorazepam 0.5mg po/PEG Midazolam 2.5mg s/c	
Pain	Drug choice depends on cause	Morphine 5-10mg po/PEG/sc	Transdermal opiate patch
Nausea / vomiting	Hyoscine butylbromide	Hyoscine butylbromide 20mg s/c	
Ventilation withdrawal	Opiates Benzodiapepines	Morphine 10mg s/c Midazolam 10mg s/c	Continuous s/c infusion

po: per oral, PEG: via gastrostomy, s/c: subcutaneous
Based on National Institute of Clinical Excellence NICE guidelines NG31 (Care of dying adults in the last days of life), APM position on Withdrawal of Ventilatory Support for Respiratory Failure at the Request of an Adult Patient [11] and Pathway for Preparing to Withdraw Non-Invasive Ventilation (NIV) in Patients with MND [14].

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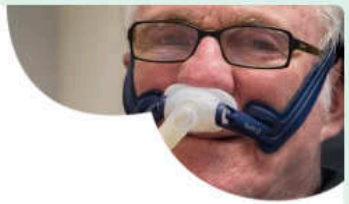
myNIV

Welcome to myNIV - a guide to using non-invasive ventilation for people living with motor neurone disease



What is NIV?

Non-invasive ventilation helps to support breathing in motor neurone disease

Getting Started

All the information and top tips you need to get started with NIV

Living with NIV

Further advice and real-life insights on making NIV work best for you

Welcome to myNIV

Using NIV can bring improvements to your daily wellbeing and give you more energy.

Why am I using NIV?

MND affects the muscles used for breathing, affecting the quality of your sleep.

How does NIV work?

Non-invasive ventilation slightly boosts the air flow into your lungs, following your natural breathing pattern.

How is my NIV controlled?

Your NIV machine is set by your care team and then locked to avoid accidental changes.