JOURNAL OF NEUROLOGY AND PSYCHOLOGY RESEARCH

CLINICAL STUDY Open Access

Amyotrophic Lateral Sclerosis: IV. Symptoms Management and Treatment

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Received date: May 16, 2025, **Accepted date:** May 22, 2025, **Published date:** May 28, 2025.

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Abstract

Amyotrophic lateral sclerosis is a complex disease which varies from person to person. It requires more research to discover effective treatments for each person living with ALS. The goal of management and treatment is to slow the disease progression, palliate and improve symptoms. and provide supportive care to improve quality of life and prolong survival. This article will review the available eleven (11) symptomatic treatments. It will also examine the four (4) FDA-approved treatments purported to slow the disease progression as well as seven (7) other treatments under research. Various other therapies will also be reviewed (physical, occupational, speech, swallowing) as well as respiratory support through invasive and non-invasive ventilation, enteral nutrition support, and mental and behavioral support. Palliative, late-stage disease management, and end-of-life care will also be discussed. Cellular therapies will lastly be considered.

Abbreviations

AAC: Augmentative alternative communication; ADL: Activities of daily living; AET: Aerobic exercise therapy; ALS: Amyotrophic lateral sclerosis; ALS-FRs: ALS-Functional rating score; ASO: Antisense oligonucleotide; BDNF: Brain-derived neurotrophic factor; BGA: Blood-gas analysis; bALS: behavioral ALS; cALS: cognitive ALS; CAM: Complementary & alternative medicine; CNF: Ciliary neurotrophic factor; COPD: Chronic obstructive pulmonary disease; CPET: cardiopulmonary PET; eFVC: erect FVC; EOL: End-of-life; FDA: (U.S.) Food & Drug Administration; FTD: Frontotemporal dementia; FVC: Forced vital capacity; HBOT: Hyperbaric oxygen therapy; HC: Hospice care; HRR: Heart rate reserve; IMV: Invasive mechanical ventilation; IV: Invasive ventilation; mRNA: mitochondrial RNA: NGT: Nasogastric tube; NIPPV: Non-invasive positive pressure ventilation; NIV: Noninvasive ventilation; NSAID: Nonsteroidal anti-inflammatory drug; OT: Occupational therapy; PC: Palliative care; PEG: Percutaneous endoscopic gastrostomy; PET: Pulmonary exercise training; PNO: Percutaneous nocturnal oximetry; PO: Pulse oximetry; PPT: Pulmonary PT; PRG: Percutaneous radiologic gastrostomy; PT: Physical therapy; RIG: Radiologically-inserted gastrostomy; RNA: Ribonucleic acid; rTMS: repetitive TMS: SCI: Spinal cord injury; sFVC: supine FVC: SNIP: Stiff nasal respiratory pressure; SOD: Superoxide sodium dismutase; SSRI: Selective serotonin reuptake inhibitor; ST: Speech therapy; TMS: Transmagnetic stimulation; UC: Usual care; VC: Vital capacity; WHO: World Health Organization.

Keywords

Amyotrophic lateral sclerosis; invasive and non-invasive ventilation; occupational therapy; palliative care; percutaneous endoscopic gastrostomy; percutaneous nocturnal oximetry; percutaneous radiologic gastrostomy; pulmonary exercise training; radiologically-inserted gastrostomy; transmagnetic stimulation.

Management and treatment

Currently, there are no known cures or treatments to stop ALS. The disease is complex and varies from person to person. Far more research is necessary to discover effective treatments for each person living with ALS.

The goal of management and treatment is to slow the disease progression, palliate and improve symptoms. and provide supportive care to improve quality of life and prolong survival. This care is best provided by multi-disciplinary teams of healthcare professionals. Attending a multidisciplinary ALS clinic is associated with longer survival, fewer hospitalizations, and improved quality of life.

Symptomatic Treatments

Medications may be used to help reduce fatigue, ease muscle cramps, control spasticity, and reduce excess saliva and phlegm (Table 1).

- Gabapantin enacarbil (Horizant): Can be used for nerve pain. It works by blocking nerve signals.
- Pregabalin (Lyrica); Can be used for nerve pain and spinal cord injury (SCI).
- Tricyclic anti-depressants (e.g., Amitriptyline): Can be used for neuropathic pain.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids: Can be used for nociceptive pain.
- Selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants: Can treat depression.
- Benzodiazepines: Can be used for anxiety.
- SSRIs and antipsychotics: While there are no medications to treat cognitive impairment/frontotemporal dementia (FTD), SSRIs and antipsychotics can help treat some of the symptoms of FTD.
- Baclofen and Tizanidine: These are the most used oral drugs for treating spasticity. An intrathecal Baclofen pump can be used for severe spasticity.
- Anticholinergics (Atropine, Scopolamine, Amitriptyline, or Glycopyrrolate): May be prescribed when people with ALS begin having trouble swallowing their saliva (sialorrhea). Can help reduce drooling.
- Mexiletine: Based on a 2106 randomized controlled trial, a 2017 review concluded that this drug is safe and effective for treating cramps in ALS
- Over-the-counter pain relievers or prescription medications like opioids: They may be used to manage pain due to muscle cramps or joint stiffness.

Drug	Use(s)	Side effects
Gabapentin	Nerve pain	Sleepiness, dizziness, headache, suicidal thoughts and actions
Pregabalin (Lyrica)	Nerve pain and spinal cord injury	Dizziness, sleepiness, h (see below), headache, tiredness, fluid retention, nausea, blurred vision, dry mouth, weight gain, difficulty concentrating, increased appetite (in children).
Tricyclic anti-depressants (Amitryptiline, Duloxetine, Cymbalta, Drizalma)	Depression, anxiety, musculoskeletal pain, neuropathic pain	Nausea, dry mouth, dizziness, drowsiness or tiredness, constipation, feeling less hungry, sweating, slowed growth, diarrhea (in children), allergic reactions
NSAIDs, acetaminophen, opioids	Nociceptive pain	Redness, itching, rash, dry skin, scaling, allergic reactions
SSRI or tricyclic antidepressants	Depression	Nausea, dry mouth, dizziness, drowsiness or tiredness, constipation, feeling less hungry, sweating, slowed growth, diarrhea (in children), allergic reactions
Benzodiazepine (Libervant)	Anxiety, apprehension, muscle spasms	Drowsiness (or sleepiness), headache, muscle weakness, trouble with balance or coordination, pain, itching, swelling, or redness
SSRI and anti-psychotics	Frontotemporal dementia	Nausea, dry mouth, dizziness, drowsiness or tiredness, constipation, feeling less hungry, sweating, slowed growth, diarrhea (in children), allergic reactions
Baclofen and Tizanidine	Spasticity	Muscle spasticity including muscle spasms due to spinal cord condition
Anticholinergics (Atropine, Scopolamine, Amitriptyline, or Glycopyrrolate)	Sialhorrea, drooling	Dry mouth, dizziness or drowsiness, blurred vision or dilated pupils, confusion, irritability or agitation, sore throat, allergies
Mexiletine (Mexitil)	Cramps, ventricular arrhythmia	Nausea and vomiting, heartburn, dizziness or lightheadedness, shaking (tremors), nervousness, trouble with coordination

Table 1: Pharmacology for ALS symptomatic treatments

Treatments to slow disease progression

FDA-approved treatments that slow the disease progression and prolong survival. Medications are also available to relieve symptoms such as fatigue, muscle cramps, spasticity, constipation, pain, and excess saliva. Depression and sleep disturbances, which are common in ALS, can be treated effectively with medication and therapy.

There are currently only four (4) treatments approved by the FDA to slow the disease progression, as detailed below. While none of these treatments have been shown to halt the progression of ALS, some people who take one or a combination of two or three may experience a positive impact on their progression (Table 2).

- **Riluzzole (Rilutek, Tiglutik, Exservan):** It modestly prolongs survival by about 2-3 months It may have a greater survival benefit for those with bulbar-onset ALS. It may work by decreasing the release of the excitatory neurotransmitter glutamate from pre-synaptic neurons. The most common side effects are nausea and a lack of energy (asthenia). People with ALS should begin treatment with Riluzole as soon as possible following their diagnosis. Riluzole is available as a tablet, liquid, or dissolvable oral film.

- **Trial Results:** There were two pivotal trials that led to the approval of Riluzole, one with 155 participants and the second with 959 participants. These trials showed a two to three-month survival benefit for people with ALS who received the active drug. More recently, a 2020 publication evaluating real world evidence of Riluzole's effectiveness indicated a median survival benefit that could range from 6 to 19 months.
- **Edavarone (Radicava):** Although approved for use in ALS in 2017, this drug had previously been used since the 1980s as a medication for stroke in Japan. For most of this time, it was available only as an intravenous infusion. However, in 2022, an oral formulation was approved for people with ALS in the U.S. and Canada. Edaravone's mechanism of action in ALS is not fully understood, but it is known to be an antioxidant and thus may reduce oxidative stress in motor neurons. It modestly slowed the decline in function in a small group of people with early-stage ALS. The most common side effects are bruising and gait disturbance.

- **Trial results:** Edavarone was approved following a phase 3 trial conducted in Japan by Mitsubishi Tanabe Pharma. Researchers observed a reduction in participants' rates of disease progression. In 2024, another company, Ferrer, reported topline results from a phase 3 randomized controlled trial (RCT) of 300 people with ALS in Europe. While still pending full results and publication, this trial showed neither a slowing of progression nor an increase in survival

- **Tofersen (Qalsody):** This genetically targeted treatment was approved for medical use in the U.S. in April 2023 for the treatment of ALS associated with a mutation in the superoxide dismutase 1 (SOD1) gene. It is an antisense oligonucleotide (ASO) that targets SOD1 mRNA to reduce the production of the SOD1 protein, which is toxic to nerve cells. A study of 108 patients with SOD1-associated ALS showed a non-significant trend towards a slowing of progression, as well as a significant reduction in neurofilament light chain, a putative ALS biomarker thought to indicate neuronal damage. A follow-up study and open-label extension suggested that earlier treatment initiation had a beneficial effect on slowing disease progression. Tofersen is available as an intrathecal injection into the lumbar cistern at the base of the spine to stop toxic SOD1proteins from being made.

- **Trial Results:** Although the phase 3 trial with 108 participants did not meet its primary functional endpoint, this drug was nonetheless approved for use by people with SOD1- ALS based on reductions in levels of neurofilaments light chain (NFL), a blood-based biomarker that is related to neurodegeneration in participants on active drug. This approval was secured through the FDA’s accelerated approval pathway, which allows the agency to approve treatments based on “surrogate endpoints” for severe diseases that lack treatments.

- **AMX-0035 (Relyvrio; Albrioza):** This additional drug, a combination of sodium phenylbutyrate and taurursodiol, received approval in the U.S. in 2022 and conditional approval in Canada based on results from a phase 2 study. Initially shown to prolong the survival of patients by an average of six months, Relyvrio was voluntarily withdrawn from the market by iots manufacturer in April 2024 following the completion of the Phase 3 PHOENIX trial after its phase 3 trial failed to meet its primary or secondary endpoints and the drug did not show substantial benefit to ALS patients.

- **Trial Results:** A phase 2 trial sponsored by Amylyx Pharmaceuticals in 137 people with ALS demonstrated evidence of a decline in the rate of progression between the active treatment and placebo groups over 24 weeks and a potential increase in survival of 5 months.

In 2025, several other promising treatments are in development, including:

- ASHA-624, which is expected to enter clinical trials. This potential disease-modifying therapy aims to slow ALS progression or even reverse motor function loss. It is designed to target the SOD1 protein. Preclinical trials are complete, and the first-in-human trial is expected to begin in early 2025.
- AMX-0114, an investigational ASO targeting the calpain-2 protein with aim to reduce its activity in the breakdown of other proteins. The Phase 1 LUMINA clinical trial in Canada is expected to begin early in 2025, with the FDA lifting the clinical hold on the Phase 1 clinical trial in the U.S.

Other notable ALS treatments and research are:

- **Monepantel (NUZ-001):** Early trial data suggest that this repurposed veterinary medication, which blocks a signaling pathway believed to contribute to ALS progression, slowed disease progression in a small Phase 1 clinical trial.
- **NDC-011:** This dual-combination therapy, consisting of Nebivolol and Donepezil, aims to reduce inflammation, protect nerve cells, and shield muscle cells from damage.
- **CSF1R Inhibitor:** Modulo Bio is developing a drug that blocks the colony stimulating factor 1 receptor (CSF1R) to reprogram microglia, the brain's immune cells, to protect neurons from damage.
- **Usnoflast:** Zydus' Phase IIb trial of Usnoflast for ALS treatment has been approved by the FDA.
- AI-Discovered Drug (FB-1006): It has advanced to clinical trials for ALS treatment.

Drug	Use(s)	Side effects
Riluzzole (Rilutek)	Slow down worsening of ALS and prolongs survival	Dizziness, drowsiness, nausea, vomiting, or numbness/tingling around the mouth Allergic reactions: Rash, itching/swelling (especially of the face/tongue/throat, dizziness, trouble breathing
Edavarone (Radicava)	Slow down worsening of ALS and prolongs survival	Bruising, problems walking, headache Allergic reactions: Rash, itching/swelling (especially of the face/tongue/throat, dizziness, trouble breathing
AMX-0035(Relyvrio)	Slow down worsening of ALS and prolongs survival	Nausea, diarrhea, decreased appetite, stomach/abdominal pain, dizziness, drowsiness, or tiredness Allergic reactions: Rash, itching/swelling (especially of the face/tongue/throat, dizziness, trouble breathing
Tofersen (Qalsody)	Slow down worsening of ALS and prolongs survival	Joint pain, muscle pain, or tiredness Allergic reactions: Rash, itching/swelling (especially of the face/tongue/throat, dizziness, trouble breathing

Table 2: Pharmacology to slow disease progression

Various other therapies

Physical therapy

Physical therapy (PT) plays a large role in rehabilitation for individuals with ALS. Specifically, physical, occupational, and speech therapists can set goals and promote benefits for individuals with ALS by delaying loss of strength, maintaining endurance, limiting pain, improving speech and swallowing, preventing complications, and promoting functional independence.

PT can promote functional independence through aerobic, range of motion, and stretching exercises. A physical therapist can help with stretching, strengthening, and preserving mobility. While physical therapy cannot stop the disease's progression, it can help maintain muscle function and reduce discomfort from immobility.

- Stretching exercises: They help maintain range of motion and prevent joint stiffness.
- Strengthening exercises: They may help with remaining muscle function but should be done cautiously to avoid overuse.

Occupational therapy

Occupational therapy (OT) and special equipment such as assistive technology can also enhance people's independence and safety throughout the course of ALS. Gentle, low-impact aerobic exercise such as performing activities of daily living, walking, swimming, and stationary bicycling can strengthen unaffected muscles, improve cardiovascular health, and help people fight fatigue and depression. Range of motion and stretching exercises can help prevent painful spasticity and shortening (contracture) of muscles. Physical and occupational therapists can recommend exercises that provide these benefits without overworking muscles because muscle exhaustion can lead to a worsening of symptoms associated with ALS, rather than providing help to people with ALS. They can suggest devices such as ramps, braces, walkers, bathroom equipment (shower chairs, toilet risers, etc.), and wheelchairs that help people remain mobile. Occupational therapists can provide or recommend equipment and adaptations to enable ALS people to retain as much safety and independence in activities of daily living as possible. Since respiratory insufficiency is the primary cause of mortality, physical therapists can help improve respiratory outcomes in people with ALS by implementing pulmonary physical therapy (PPT). This includes inspiratory muscle training, lung volume recruitment training, and manual assisted cough therapy aimed at increasing respiratory muscle strength as well as increasing survival rates.

OT can assist with activities of daily living through adaptive equipment. An occupational therapist can provide strategies and assistive devices to help patients maintain independence for as long as possible. This may include adaptive devices for eating, dressing, and bathing, as well as recommendations for home modifications to improve safety and mobility.

Speech therapy

Speech therapy (ST) can assist people with ALS who have difficulty speaking. A speech therapist can help patients manage problems with speech and communication, often recommending strategies for clearer speech and the use of communication aids (e.g., computer-based speech devices) as the disease progresses.

People with ALS who have difficulty speaking or swallowing may benefit from working with a speech-language pathologist. These health professionals can teach people adaptive strategies such as techniques to help them speak louder and more clearly. As ALS progresses, speech-language pathologists can recommend the use of augmentative and alternative communication such as voice amplifiers, speech-generating devices (or voice output communication devices), or low-tech communication techniques such as head-mounted laser pointers, alphabet boards or yes/no signals.

Swallowing therapy

Dysphagia is a common symptom of ALS, and a speech or swallowing therapist can offer exercises and techniques to help with swallowing. In some cases, a feeding tube may be recommended if swallowing becomes too difficult.

Respiratory support

Breathing support can be provided in the form of non-invasive or invasive therapies, resulting in both improved quality and length of life. Devices such as a cough-assist machine can help clear mucus and prevent respiratory infections.

Non-invasive ventilation

Non-invasive ventilation (NIV) is the primary treatment for respiratory failure in ALS and was the first treatment shown to improve both survival and quality of life. It uses a face or nasal mask connected to a ventilator that provides intermittent positive pressure to support breathing. Continuous positive pressure is not recommended for people with ALS because it makes breathing more difficult. Initially, NIV is used only at night because the first sign of respiratory failure is decreased gas exchange (hypoventilation) during sleep; symptoms associated with this nocturnal hypoventilation include interrupted sleep, anxiety, morning headaches, and daytime fatigue. As the disease progresses, people with ALS develop shortness of breath when lying down, during physical activity or talking, and eventually at rest. Other symptoms include poor concentration, poor memory, confusion, respiratory tract infections, and a weak cough. Respiratory failure is the most common cause of death in ALS.

It is important to monitor the respiratory function of people with ALS every three months because beginning NIV soon after the start of respiratory symptoms is associated with increased survival. This involves asking the person with ALS if they have any respiratory symptoms and measuring their respiratory function. The most used measurement is upright forced vital capacity (FVC), but it is a poor detector of early respiratory failure and is not a good choice for those with bulbar symptoms, as they have difficulty maintaining a tight seal around the mouthpiece. Measuring FVC while the person is lying on their back (supine FVC) is a more accurate measure of diaphragm weakness than upright FVC. Sniff nasal inspiratory pressure (SNIP) is a rapid, convenient test of diaphragm strength that is not affected by bulbar muscle weakness. If someone with ALS has signs and symptoms of respiratory failure, they should undergo daytime blood gas analysis (BGA) to look for hypoxemia (low oxygen in the blood) and hypercapnia (too much carbon dioxide in the blood). If their daytime BGA is normal, they should then have nocturnal pulse oximetry (PO) to look for hypoxemia during sleep.

NIV prolongs survival longer than Riluzole. A 2006 randomized controlled trial found that NIV prolongs survival by about 48 days and improves the quality of life; however, it also found that some people with ALS benefit more from this intervention than others. For those with normal or only moderately impaired bulbar function, NIV prolongs survival by about seven months and significantly improves the quality of life. For those with poor bulbar function, NIV neither prolongs survival nor improves the quality of life, though it does improve some sleep-related symptoms. Despite the clear benefits of NIV, about 25–30% of all people with ALS are unable to tolerate it, especially those with cognitive impairment or bulbar dysfunction. Results from a large 2015 cohort study suggest that NIV may prolong survival in those with bulbar weakness, so NIV should be offered to all people with ALS, even if it is likely that they will have difficulty tolerating it.

Invasive ventilation

Invasive ventilation (IV) is an option for people with advanced ALS when NIV is not enough to manage their symptoms. While IV prolongs survival, disease progression and functional decline continue. It may decrease the quality of life of people with ALS or their caregivers.

IV bypasses the nose and mouth (the upper airways) by making a cut in the trachea (tracheostomy) and inserting a tube connected to a ventilator. It is an option for people with advanced ALS whose respiratory symptoms are poorly managed despite continuous NIV use. While IV prolongs survival, especially for those younger than 60, it does not treat the underlying neurodegenerative process.

The person with ALS will continue to lose motor function, making communication increasingly difficult and sometimes leading to locked-in syndrome (LIS), in which they are completely paralyzed except for their eye muscles. About half of the people with ALS who choose to undergo IV report a decrease in their quality of life but most still consider it to be satisfactory. However, IV imposes a heavy burden on caregivers and may decrease their quality of life. Attitudes toward IV vary from country to country; about 30% of people with ALS in Japan choose IV versus less than 5% in North America and Europe.

Clinical practice

Respiratory complications are the main cause of death in ALS, primarily because of diaphragmatic weakness combined with aspiration and infection. Erect forced vital capacity (eFVC) and vital capacity (VC) are the most widely used tests to evaluate respiratory function and should be performed regularly, along with an assessment of symptoms suggestive of respiratory insufficiency. SNP may be more accurate in patients with weak lips, but neither forced vital capacity nor SNP is a sensitive predictor of respiratory insufficiency in patients with severe bulbar involvement. Percutaneous nocturnal oximetry (PNO) is an easy tool to screen patients and can be useful to determine the need for non-invasive positive-pressure ventilation (NIPPV). Phrenic nerve responses may predict hypoventilation in ALS. Blood gas abnormalities are generally a late finding. Cough effectiveness can be assessed by measuring peak cough flow. Table 3 summarizes the symptoms and signs of respiratory insufficiency whereas Figure 1 is a flowchart for the management of respiratory dysfunction.

Symptoms	Signs
Dyspnea on minor exertion or talking	Tachypnea
Orthopnea	Use of auxiliary respiratory muscles
Frequent nocturnal awakenings	Paradoxical movement of the abdomen
Excessive daytime sleepiness	Decreased chest wall movement
Daytime fatigue	Weak cough
Morning headache	Sweating
Difficulty clearing secretions	Tachycardia
Apathy	Morning confusion, hallucinations
Poor appetite	Weight loss
Poor concentration and/or memory	Mouth dryness

Source: Modified from Leigh et al.

Table 3: Symptoms and signs of respiratory insufficiency in ALS

NIPPV and, less frequently, invasive mechanical ventilation (IMV) are used to alleviate symptoms of respiratory insufficiency and prolong survival (Table 4). There is no clear evidence regarding the timing and criteria for use of NIPPV and IMV in patients with ALS. The use of mechanical ventilation varies between countries, reflecting economic and cultural differences. Ideally, the patient’s advance directives and a plan for management of respiratory insufficiency should be established before respiratory complications occur.

Symptoms/signs related to respiratory muscle weakness	At least one of the following
	Dyspnea
	Tachypnea
	Orthopnea
	Disturbed sleep due to nocturnal desaturation/ arousals
	Morning headache
	Use of auxiliary respiratory muscles at rest
	Paradoxical respiration
	Daytime fatigue
	Excessive daytime sleepiness (ESS>9)
Abnormal respiratory function tests	**At least one of the following**
	Forced vital capacity <80% of predicted value
	Sniff nasal pressure <40 cm H_2O
	PI max <60 mm H_2O
	Significant nocturnal desaturation on overnight oximetry
	Morning blood gas pCO2>45 mmHg

Figure 1: Flowchart for the management of respiratory dysfunction

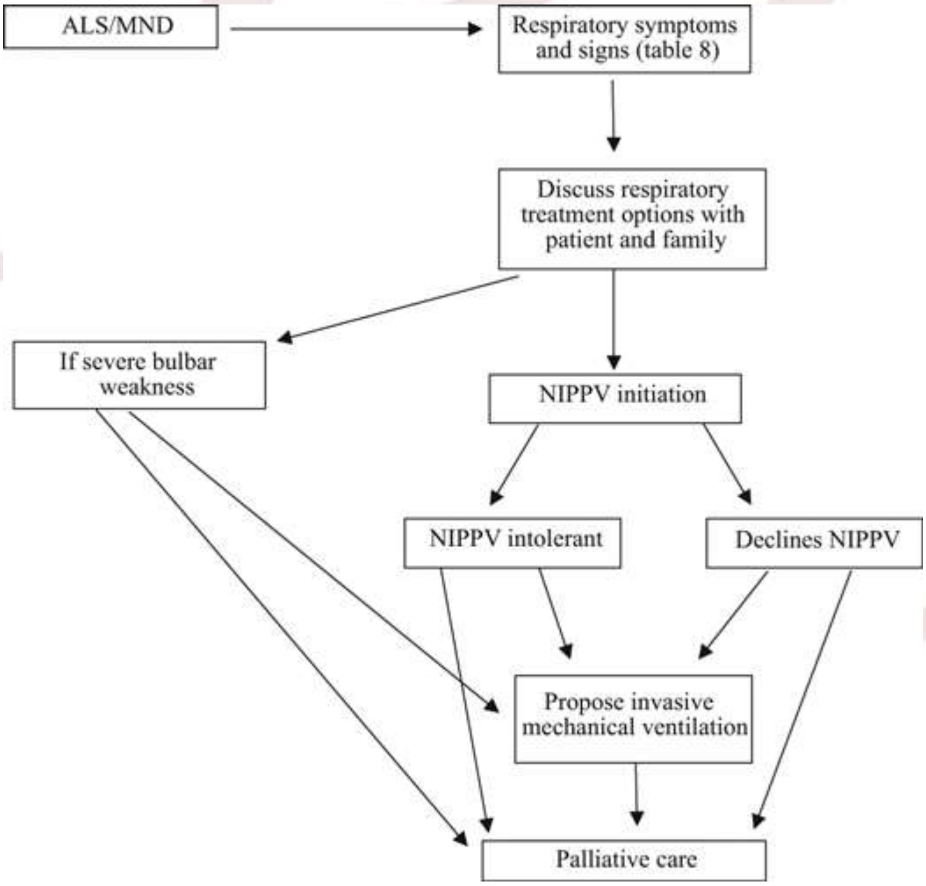

Figure 1: Flowchart for the management of respiratory dysfunction

NIPPV increases survival and improves patients' quality of life and is the preferred therapy to alleviate symptoms of respiratory insufficiency (see Table 5). Treatment is usually initiated at night to alleviate symptoms of nocturnal hypoventilation. NIPPV improves quality of life and prolongs survival in patients presenting with respiratory insufficiency, although this has not been confirmed in patients with bulbar onset disease. Patients with bulbar palsy are less compliant with NIPPV, due in part to increased secretions. The use of diaphragmatic pacing or respiratory exercises in ALS is not established.

Invasive mechanical ventilation can prolong survival in ALS, in some cases for many years. However, no documented improvement in quality of life has been reported, and there is a risk that some patients will develop a 'locked-in' state. The availability and cultural acceptability of IMV in patients with ALS varies greatly between different countries and cultures. It is costly and has significant emotional and social impacts on patients and caregivers.

Advantages	**Drawbacks**	**Ethics**
Increases survival time	Generates more bronchial secretions	Ethical issues regarding discontinuation
Prevents aspiration	Increases risk of infection	
Ability to provide more effective ventilator pressures and better gas exchange	Introduces risk of tracheo-esophageal fistula, tracheal stenosis or tracheomalacia	
	Greatly increased costs	
	Increased family and carer burden, including 24-h nursing requirement	

Table 5: Advantages, drawbacks and ethics of invasive mechanical ventilation

Parenteral morphine, a benzodiazepine and an antiemetic are used when the patient decides that ventilatory support should be withdrawn. There is Class I evidence for the use of opioids and/or oxygen to treat dyspnea in patients with terminal cancer or chronic obstructive pulmonary disease (COPD), but no controlled studies in ALS exist.

Improving the clearance of bronchial secretions is important in patients with ALS to promote quality of life, improve NIV tolerance and decrease the risk of infection. Cough-assisting devices and chest wall oscillation may be of value.

Recommendations

1. Symptoms or signs of respiratory insufficiency (including symptoms of nocturnal hypoventilation) should be checked at each visit (GCPP).

2. Forced vital capacity and vital capacity are the most available and practical tests for the regular monitoring of respiratory function (GCPP).

3. SNP may be used for monitoring, particularly in bulbar patients with weak lips (GCPP).

4. Percutaneous nocturnal oximetry is recommended as a screening test and for monitoring respiratory function (GCPP).

5. Symptoms or signs of respiratory insufficiency should prompt discussions with the patient and caregivers about treatment options and the terminal phase. Early discussions are needed to allow advance planning and directives (GCPP).

6. NIPPV should be considered in preference to IMV in patients with symptoms or signs of respiratory insufficiency (GCPP).

7. NIPPV can prolong survival for many months (level A) and may improve the patient's quality of life (level C).

8. Active management of secretions and provision of cough-assist devices can increase the effectiveness of assisted ventilation in ALS (GCPP).

9. IMV has a major impact upon caregivers and should be initiated only after informed discussion (GCPP).

10. Unplanned (emergency) IMV should be avoided through an early discussion of end-of-life issues, co-ordination with palliative care teams and appropriate advance directives (GCPP).

11. Oxygen therapy alone should be avoided as it may exacerbate carbon dioxide retention and oral dryness. Use oxygen only if symptomatic hypoxia is present (GCPP).

12. The medical treatment of intermittent dyspnea should involve: (a) For short dyspneic bouts: relieve anxiety and give lorazepam 0.5–2.5mg sublingually; (b) For longer phases of dyspnea (>30min): give morphine 2.5 mg orally or s.c. (GCPP).

13. For the medical treatment of chronic dyspnea, start with morphine 2.5 mg orally four to six times daily. For severe dyspnea, give morphine s.c. or as an IV infusion. Start with 0.5 mg/h and titrate. If needed, add Midazolam (2.5–5 mg) or Diazepam for nocturnal symptom control and to relieve anxiety (GCPP).

Enteral nutrition support

Weight loss at time of diagnosis is an independent prognostic factor of survival in ALS. Data indicate that patients with ALS have an increased resting energy expenditure. The initial management of dysphagia is based on the following: dietary counseling, modification of food and fluid consistency (blending food, adding thickeners to liquids), prescription of high-protein and high-caloric supplements, education of the patient and carers in feeding and swallowing techniques such as supraglottic swallowing and postural changes and flexing the neck forward on swallowing to protect the airway ('chin-tuck maneuver'). Some patients with difficulty swallowing tap water can more easily drink carbonated fluids and/or ice-cold liquids. When tube feeding is needed, three procedures obviate the need for major surgery and general anesthesia: percutaneous endoscopic gastrostomy (PEG), percutaneous radiologic gastrostomy (PRG), or radiologically inserted gastrostomy (RIG), and nasogastric tube (NGT) feeding.

PEG is the standard procedure for enteral nutrition in ALS and is widely available. It improves nutrition, but there is no convincing evidence that it prevents aspiration or improves quality of life or survival (Class III). The procedure requires mild sedation and is therefore more hazardous in patients with respiratory impairment and/or at an advanced stage of the disease.

As the disease progresses, patients may require feeding tubes and ventilator assistance. Preventing weight loss and malnutrition in people with ALS improves both survival and quality of life. Initially, difficulty swallowing (dysphagia) can be managed by dietary changes and swallowing techniques.

Difficulties with chewing and swallowing make eating very difficult (dysphagia) and increase the risk of choking or of aspirating food into the lungs. In later stages of the disorder, aspiration pneumonia can develop, and maintaining a healthy weight can become a significant problem that may require the insertion of a feeding tube. As the diaphragm and intercostal muscles of the rib cage that support breathing weaken, measures of lung function such as vital capacity and inspiratory pressure diminish. In respiratory-onset ALS, this may occur before significant limb weakness is apparent. Individuals affected by the disorder may ultimately lose the ability to initiate and control all voluntary movement, known as locked-in syndrome. Bladder and bowel function are usually spared, meaning urinary and fecal incontinence are uncommon, although trouble getting to a toilet can lead to difficulties. The extraocular muscles responsible for eye movement are usually spared, meaning the use of eye tracking technology to support augmentative communication is often feasible, albeit slow, and needs may change over time. Despite these challenges, many people in an advanced state of disease report satisfactory wellbeing and quality of life.

Preventing weight loss and malnutrition in people with ALS improves both survival and quality of life. Weight loss in ALS is often caused by muscle wasting and increased resting energy expenditure. Weight loss may also be secondary to reduced food intake since dysphagia develops in about 85% of people with ALS at some point throughout their disease course. Therefore, regular periodic assessment of the weight and swallowing ability in people with ALS is very important. Dysphagia is often initially managed via dietary changes and modified swallowing techniques. People with ALS are often instructed to avoid dry or chewy foods in their diet and instead have meals that are soft, moist, and easy to swallow. Switching to thick liquids (like fruit nectar or smoothies) or adding thickeners (to thin fluids like water and coffee) may also help people facing difficulty swallowing liquids. There is tentative evidence that high-calorie diets may prevent further weight loss and improve survival, but more research is still needed.

A feeding tube should be considered if someone with ALS loses 5% or more of their body weight or if they cannot safely swallow food and water. This can take the form of a gastrostomy tube, in which a tube is placed through the wall of the abdomen into the stomach, or (less commonly) a nasogastric tube, in which a tube is placed through the nose and down the esophagus into the stomach. A gastrostomy tube is more appropriate for long-term use than a nasogastric tube, which is uncomfortable and can cause esophageal ulcers. The feeding tube is usually inserted by percutaneous endoscopic gastrostomy (PEG). While there is weak evidence that PEG tubes improve survival in people with ALS, no randomized clinical trials (RCTs) have yet been conducted to indicate whether enteral tube feeding has benefits compared to continuation of feeding by mouth. Nevertheless, PEG tubes are still offered with the intent of improving the person's quality of life by sustaining nutrition, hydration status, and medication intake.

Non-invasive ventilation during the PEG procedure may be feasible in patients with respiratory impairment (Class IV). The timing of PEG is mainly based on symptoms, nutritional status and respiratory function. To minimize risks, PEG should be performed before vital capacity falls below 50% of predicted (Class IV). PRG is a newer alternative to PEG and has the major advantage that it does not require patient sedation for insertion. PRG may be as satisfactory and better tolerated than PEG, but PRG is not widely available. NGT insertion is a minor procedure that can be performed on all patients, but it can have drawbacks such as increasing oropharyngeal secretions or causing nasopharyngeal discomfort or even ulceration. Recent studies suggest that home parenteral nutrition is possible as an alternative to enteral feeding in patients with advanced ALS and poor respiratory function (Class IV).

A nutritionist can help design a diet that meets the person’s nutritional needs while accommodating for any swallowing or chewing difficulties.

Recommendations

1. Bulbar dysfunction and nutritional status, including body weight, should be checked at each visit. Difficulty drinking tap water is frequently the first sign of significant dysphagia (GCPP).

2. Patients should be referred to a dietitian as soon as dysphagia appears. A speech and language therapist can give valuable advice on swallowing techniques (GCPP).

3. The timing of PEG/PRG is based on an individual approach considering bulbar symptoms, malnutrition (weight loss of over 10%), respiratory function and the patient's general condition. Early insertion of a feeding tube is recommended (GCPP).

4. When PEG is indicated, patient and carers should be informed: (i) of the benefits and risks of the procedure; (ii) that it is possible to continue to take food orally as long as it is possible; and (iii) that deferring PEG to a late disease stage may increase the risk of the procedure (GCPP).

5. PRG is a suitable alternative to PEG. This procedure can be used as the procedure of choice or when PEG is deemed hazardous (GCPP).

6. Tubes with relatively large diameter (e.g. 18–22 Charrière) are recommended for both PEG and PRG to prevent tube obstruction (GCPP).

7. Prophylactic medication with antibiotics on the day of the operation may reduce the risk of infection (GCPP).

8. NGT feeding may be used in the short-term and when PEG or PRG is not suitable (GCPP).

9. Home parenteral nutrition may be used in patients with advanced ALS (GCPP).

Mental health support

ALS can take a significant emotional toll, so counseling or therapy may be beneficial for both the individual with ALS and their family members. Support groups, whether in person or online, can also provide emotional support and practical tips for living with the disease.

ALS is associated with a frontotemporal syndrome in a significant proportion of cases, and these patients have a shorter survival (Class IV). Approximately 5–15% of patients with ALS meet the diagnostic criteria for frontotemporal dementia (FTD), typically frontal variant with executive dysfunction and behavior change (Class III) although progressive aphasias have been described. A further third of patients show mild cognitive (cALS) and/or behavioral (bALS) impairment. cALS is associated with early deficits in verbal (letter) fluency and a mild dysexecutive syndrome (Class III). Language changes are sometimes reported as are symptoms of memory impairment, but these are more likely due to an encoding rather than a retention deficit. bALS shows behavior change that partially meets criteria for FTD, with apathy most reported (Class IV). Impairment in emotional and social cognition has also been described (Class III). Cerebral atrophy on magnetic resonance imaging or ocular fixation instabilities may be biomarkers of behavioral and cognitive abnormalities (Class III).

Carers may be unaware of mild impairment as increasing physical disability results in a loss of autonomy and a greater reliance on others for daily tasks. Executive dysfunction may manifest as difficulties in managing affairs/finances, planning for the future, making decisions and learning new tasks, including the use of equipment associated with symptomatic treatment for ALS (e.g. gastrostomy, NIV).

Recommendations

1. A frontotemporal syndrome occurs in up to half of patients with ALS (level B) and is associated with a poorer prognosis. Symptoms of cognitive dysfunction may appear before or after the onset of motor symptoms.

2. The Mini-Mental State Examination (MMSE) is an insensitive test for cALS and bALS.

3. Rapid screening tools that include tests of verbal fluency can identify patients in whom more detailed neuropsychological evaluation is mandated (level C).

4. In all patients with frontal dysexecutive syndromes, care needs to be taken to ensure informed consent during decision-making; capacity issues may need to be considered (GCPP).

5. Carers/ /healthcare professionals should be informed of the symptoms of dysexecutive syndrome and trained in their management (GCPP).

Communication in patients with ALS

Most clinically apparent communication difficulties in ALS result from dysarthria. However, subtle changes in language function may also occur, as evidenced by reduced verbal output, reduced spelling ability, increased word-finding difficulties and impaired auditory comprehension of specific classes of language (e.g. verbs more than nouns) and more complex language constructs. Deficits may be subtle and only identifiable with formal neuropsychological testing. Language impairment can reduce the quality of life of both patients and carers and can make clinical management difficult (Class IV). Formal neuropsychological evaluation and support may be required in patients with concomitant evolving language deficits. The overall goal should be to optimize the effectiveness of communication, concentrating on meaningful interpersonal communication with the primary carer and family. This should include strategies for effective conversation and the introduction of alternative communication devices where appropriate.

Augmentative and alternative communication systems can substantially improve the quality of life for both patients and carers. Prosthetic treatments (palatal lift and/or a palatal augmentation prosthesis) can be useful in the reduction of hypernasality and improvement of articulation, but no formal comparative studies in ALS exist. For those requiring full mechanical ventilation, eye-pointing, eye-gaze or head-tracking, augmentative high-tech communication devices may be useful.

Recommendations

1. Regular assessment (i.e. every 3–6 months) of speech and language function by a trained speech and language therapist is recommended (GCPP).

2. Those with evidence of early language deficits should undergo full neuropsychological testing (GCPP).

3. The use of appropriate communication support systems (ranging from pointing boards with figures or words, to computerized speech synthesizers) should be individualized and appropriate training and support provided as required (GCPP).

Assistive devices and technologies

Assistive devices and technologies may include:

- Mobility aids: As mobility declines, assistive devices like walkers, wheelchairs, or power scooters can help maintain independence.

- Communication aids: For patients who lose the ability to speak, augmentative and alternative communication (AAC) devices, such as tablets with speech-generating software or eye-tracking systems, can help people communicate effectively.

- Environmental modifications: Home adaptations like ramps, grab bars, and stairlifts can make life easier and safer for those with limited mobility.

Palliative and end-of-life care

Hospice care (HC), or palliative care (PC) at the end of life, is especially important in ALS because it helps to optimize the management of symptoms and increases the likelihood of a peaceful death. It focuses on improving the quality of life by managing symptoms such as pain, breathing difficulties, and emotional distress. Hospice care can improve symptom management at the end of life and increase the likelihood of a peaceful death. It can be provided alongside curative treatments and is available at any stage of ALS. Whereas it relieves symptoms and improves the quality of life, it does not treat the underlying disease.

It should begin shortly after someone is diagnosed with ALS.A palliative care approach should be incorporated into the care plan for patients and carers from the time of diagnosis. The aim of palliative care is to maximize the quality of life of patients and families by relieving symptoms, providing emotional, psychological and spiritual support as needed, removing obstacles to a peaceful death and supporting the family in bereavement. Early referral to a specialist palliative care team is appropriate. Palliative care based in the community or through hospice contacts (e.g. home care teams) can proceed in partnership with clinic-based neurological multidisciplinary care. A small proportion of patients with ALS express interest in assisted suicide and may choose euthanasia where it is legalized.

It is unclear exactly when the end-of-life (EOL) phase begins in ALS, but it is associated with significant difficulty moving, communicating, and, in some cases, thinking. Although many people with ALS fear choking to death (suffocating), they can be reassured that this occurs rarely, less than 1% of the time. Most patients die at home,] and in the final days of life, opioids can be used to treat pain and dyspnea, while benzodiazepines can be used to treat anxiety.

Early discussion of EOL issues gives people with ALS time to reflect on their preferences for end-of-life and can help avoid unwanted interventions or procedures. Once they have been fully informed about all aspects of various life-prolonging measures, they can fill out advance directives indicating their attitude toward noninvasive ventilation, invasive ventilation, and feeding tubes. Late in the disease course, difficulty speaking due to muscle weakness (dysarthria) and cognitive dysfunction may impair their ability to communicate their wishes regarding care.

Continued failure to solicit the preferences of the person with ALS may lead to unplanned and potentially unwanted emergency interventions, such as invasive ventilation. If people with ALS or their family members are reluctant to discuss EOL issues, it may be useful to use the introduction of gastrostomy or noninvasive ventilation as an opportunity to bring up the subject. In the final days of life, opioids can be used to treat pain and dyspnea, while benzodiazepines can be used to treat anxiety.

Death is usually caused by respiratory failure. Discussion of end-of-life issues gives people with ALS time to reflect on their preferences for end-of-life care and can help avoid unwanted interventions or procedures.

Recommendations

1. Whenever possible, offer input from a palliative care team early in the course of the disease.

2. Initiate discussions on end-of-life decisions when the patient asks or provides an opportunity for discussion on the provision of end-of-life information and/or interventions.

3. Discuss the options for respiratory support and end-of-life issues if the patient has dyspnea, other symptoms of hypoventilation or a forced vital capacity below 50%.

4. Inform the patient of the legal situation regarding advance directives and the naming of a healthcare proxy. Offer assistance in formulating an advance directive (GCPP).

5. Re-discuss the patient's preferences for life-sustaining treatments every 6 months (GCPP).

6. Initiate early referral to hospice or homecare teams well in advance of the terminal phase of ALS (GCPP).

7. Be aware of the importance of spiritual issues for the quality of life and treatment choice. Establish a liaison with local pastoral care workers to be able to address the needs of the patient and relatives (GCPP).

8. For the symptomatic treatment of dyspnea and/or intractable pain, use opioids alone or in combination with benzodiazepines if anxiety is present. Titrating the dosages against the clinical symptoms will rarely if ever result in life-threatening respiratory depression (GCPP).

9. Terminal restlessness and confusion because of hypercapnia can be treated with neuroleptics (e.g. Chlorpromazine 12.5 mg every 4–12 h p.o., i.v., or p.r.) (GCPP).

10. Use oxygen only if symptomatic hypoxia is present (GCPP).

Late-stage disease management

Late-stage disease management involves:

Advanced care planning:

- **End-of-life discussions:** It is important to have open conversations with healthcare providers and family about future care needs, such as whether to pursue ventilatory support, the use of feeding tubes, and advanced directives. Discussing options for hospice or palliative care can also provide comfort as the disease progresses.

- **Legal and financial planning:** People with ALS may consider seeking legal advice to create or update living wills, power of attorney, and financial plans to ensure that their wishes are followed.

Unproven therapies

Patients with ALS frequently use complementary and alternative medicines (CAM) such as vitamins, herbal supplements, homoeopathy and acupuncture. Series of Class IV trials have tested interferon-alfa, human recombinant SOD1, ciliary neurotrophic factor (CNF), brain-derived neurotrophic factor (BDNF) and similar drugs, all without evidence of clinical benefit. Insulin-like growth factor-1 has been injected intrathecally safely, with a modest clinical effect reported (Class IV). In randomized, controlled and open studies, liquorpheresis (filtration of cerebrospinal fluid) has been performed in 11 patients with ALS, without clinical effect (Class IV). A Phase 1 safety study of hyperbaric oxygen therapy (HBOT) reported some efficacy on fatigue in four of five patients with ALS, whilst a phase II study was reported as negative (Class IV). Repetitive transcranial magnetic stimulation (rTMS) of the motor cortex had a beneficial effect in a pilot trial (Class IV) but did not delay functional deterioration in a double-blind placebo-controlled study in 20 patients (Class III).

Cellular therapies

Stem cell therapy is still in experimental development in ALS. The intravenous, intrathecal or intraparenchymal administration of hematopoietic stem cells derived from peripheral blood or bone marrow has been tested in small series of patients (Class IV). Even if these procedures are safe in the short term, the studies to date have not yielded sufficiently robust data to allow translation to clinical practice. Clinical efficacy is unproven, and long-term safety still needs to be demonstrated.

Several patients with ALS have, in a non-scientific setting, received intracerebral transplantation of olfactory ensheathing cells, resulting in serious side effects in some (Class IV).

Recommendations

1. Before cellular therapies become a reality, a more thorough preclinical evaluation and elucidation of several open questions is mandatory (GCPP).

2. No well-designed clinical trials testing cellular therapies have yet been completed demonstrating safety and clinical efficacy supported by pathological evidence in a sufficient number of patients.

3. Patients with ALS should be carefully informed about existing reliable data related to cell therapies. All current treatments with cell transplantation are purely experimental, and there is no proven effect on disease outcome. If they decide to undergo transplantation, thorough examination before and after the stem cell treatment should be performed and documented to improve the knowledge of benefits and/or side effects (GCPP).

4. Accurate and unbiased information related to cell therapies and other unproven/ alternative therapies needs to be delivered to the patient community (GCPP).

4. All procedures involving the injection and transplantation of stem cells to a patient with ALS should be considered experimental and should be approved by a medical research ethical review board and performed in full accordance with the Declaration of Helsinki (WMA, 1964) (GCPP).

Conclusions and take-aways

- While ALS remains an incurable disease, a multidisciplinary approach can help manage symptoms and improve the quality of life for both the person with ALS and their caregivers. Treatment plans are highly individualized, and it is important for people with ALS to work closely with a team of healthcare providers, including neurologists, physical and occupational therapists, speech therapists, and respiratory specialists.

- A growing number of ALS clinics are deploying multidisciplinary teams to care for and meet the physical, emotional, and nutritional needs of people with ALS. These palliative care teams include physical, respiratory, speech, and occupational therapists to help people with ALS breathe easier, keep moving, and stay connected.

- The goal of management and treatment is to slow the disease progression, improve symptoms and provide supportive care to improve quality of life and prolong survival.

- Symptomatic treatments and treatments to slow disease progression have been presented along with the available pharmacology.
- The several therapies have also been discussed including physical, occupational, speech, and swallowing therapies.
- Respiratory support in terms of invasive and non-invasive ventilation was explored. Other support (nutritional, psychological) was also included.
- Assistive devices and technology, hospice care, late-stage disease management, and end-of-life care were also covered.

Sidebar 1 - Exercise and ALS

In 2012, the ALS Therapy Development Institute discussed the potential benefits of exercise for people living with ALS. Since then, more studies have been conducted to fully explore and better understand whether an exercise routine can provide any benefit to those living with ALS.

(Disclaimer: The study conclusions expressed in this Sidebar should not be taken as medical advice. Please talk to your medical providers before beginning any form of exercise routine.)

Exercise in early-stage ALS

In 2014 a study was published by Kamide et al. titled "Identification of the type of exercise therapy that affects functioning in patients with early-stage Amyotrophic Lateral Sclerosis". It retrospectively collected data from medical records on 156 people with ALS who were prescribed exercise therapy by physical therapists between 2001 and 2011 at six institutions in Japan. Data including age, sex, site of onset and disease duration were collected along with the ALS Functional Rating Score -Revised (SFRS-R) scores at baseline and during exercise therapy.

The type of exercise therapy prescribed and the number of visits to a physical therapist were also noted. The types of exercise therapies prescribed included stretching, resistance training, cycle ergometer training, standing training, walking training, activities of daily life (ADL) training and respiratory physical therapy.

Both resistance training and cycle ergometer training were found to have no effect on function in early-stage ALS patients. No studies prior to this one had been reported on cycle ergometer training so results could not be compared, however two previous studies had investigated the effect of resistance training. The previous studies on resistance training found that it alleviated functional decline in early-stage ALS patients. In the previous studies, participants with rapid disease progression were suspected to be withdrawn from the analysis whereas in the current study they were included. Because of this, it appears that resistance training might not be generalizable to all people with ALS.

When prescribed together, ADL training and walking training appeared to significantly alleviate functional decline in participants. However, the participants who did not carry out both were found to have a small functional decline. No explanation was found as to why this was.

The fact that the study relied on information collected from medical records from the past and did not have active participants was a major limitation that did not allow for bias to be controlled sufficiently. Both frequency and intensity of exercise sessions were not clearly regulated and could not be set to one standard across the board. Also, sufficient data on the use of Riluzole was unable to be collected to measure its impact. Taking this into consideration, the researchers still concluded that exercise therapy in which walking training and ADL training are combined alleviates functional decline for early-stage ALS patients.

Using cardiopulmonary exercise testing to define exercise

In 2018, Braga et al. (2) published a paper titled "The role of moderate aerobic exercise as determined by cardiopulmonary exercise testing in ALS". The study consisted of 48 people living with ALS split into two groups – 24 in the exercise group and 24 in the no exercise group. In the exercise group, Cardiopulmonary Exercise Testing (CPET) was used to determine the intensity at which everyone would exercise at, so as not to overexert the muscles.

The results of the study showed that a strictly monitored moderate exercise program may significantly reduce motor deterioration in people with ALS. At a checkup six months after the exercise sessions were completed, it was found that the exercise group had a significantly higher ALSFRS-R spinal sub-score and that the mean difference of functional decline expressed on the ALSFRS-Total score between groups also showed a small but positive effect favoring the exercise group.

Despite the limited sample size, the authors of that study concluded that moderate exercise protocol with CPET evaluations can be safe and beneficial and should be considered in the multidisciplinary approach to ALS patients. When prescribed and supervised appropriately, it can be physically and psychologically important for people with ALS, particularly those in the early stages of the disease before significant muscle atrophy has set in. Strengthening exercises with low to moderate weights and aerobic exercises such as swimming, walking and bicycling at submaximal levels may be important components of an overall management plan even if they might not improve the muscle strength of muscles already weakened by ALS.

Exercise potentially improves quality of life for people with ALS

In 2019, Ferri et al. published a paper titled "Tailored exercise training counteracts muscle disuse and attenuates reductions in physical function in individuals with amyotrophic lateral sclerosis." The study consisted of 15 people with ALS – 8 in an exercise group (TRAIN) and 8 in a standard care group (UC). The exercise regimen consisted of three sessions a week for 12 weeks. Exercise consisted of cycling, strength exercises, proprioceptive exercises and upper/lower extremity stretching exercises. Intensity of exercise was adjusted to the individual.

Like Braga et al., this study conducted CPET at baseline and following the 12-week training program. On top of this the ALSFRS-R, ALS Severity Scale (ALS-SS) and McGill Quality of Life (QoL) questionnaire were also measured.

The results of the study showed that a combined moderate aerobic and strength training program was not only safe but also beneficial for physical function and aerobic fitness of the participants. Based on these results, the researchers concluded that tailored moderate intensity exercise is likely not detrimental for people living with ALS and can counteract muscle disuse.

Does potential aerobic exercise therapy benefits apply to everyone with ALS?

Another study, *"Aerobic exercise therapy in ambulatory patients with ALS: A randomized controlled trial,"* was published by van Groenestijn et al. in 2019. This study was one part of a larger ALS related study, which looked at the effects of Aerobic Exercise Therapy (AET) as well as Cognitive Behavioral Therapy (CBT) on people with ALS.

For this study the AET consisted of three sessions a week – two at home and one conducted at a rehabilitation center or academic hospital supervised by specially trained intervention physiotherapists - for 16 weeks. The at home sessions consisted of individually tailored AET on a cycle ergometer or step board with intensity gradually increasing from 50% (moderate) to 75% (vigorous) heart rate reserve (HRR) and duration gradually increased from 20 to 35 minutes. The supervised sessions lasted one hour and consisted of individually tailored aerobic exercise training and muscle strengthening exercises.

There were 57 total participants split into two groups: 27 in the AET group and 30 in the Usual Care (UC) group. However, only 10 participants from the AET group completed the full AET program and the subsequent follow ups. For the UC group, 22 participants completed the entirety of the study. The participants who completed the full AET program were characterized by a relatively slow disease progression and a longer survival probability. The findings support the idea that AET may have a potential protective effect among "slow progressors".

However, because of the large number of participants who were unable or unwilling to complete the exercise program, the researchers did not recommend making AET part of UC as it is not accessible to every person with ALS but they do recommend keeping an active lifestyle according to the World Health Organization (WHO) Global Recommendations on Physical Activity for Health.

In summary, the above studies tend to agree that exercise is not detrimental to people living with ALS and may provide benefits. Nevertheless, limitations on these studies, such as small sample sizes or being retrospective, make it hard to determine whether this is generalizable across all people living with ALS.

References

1. Alexander E (2014). "George Bush delivers possibly the best ALS ice bucket challenge yet". The Independent.

2 (The) Amyotrophic Lateral Sclerosis (ALS) Association (2023). "FDA-approved drugs for treating ALS".

3. (The) Amyotrophic Lateral Sclerosis (ALS) Association (2023). "AMX0035 (RELYVRIO)".

4. Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, Damme van P, et al. (March 2012). "EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force". European Journal of Neurology. 19(3):360–75. doi:10.1111/j.1468-1331.2011.03501.x.

5. AP News (2024). "ALS drug will be pulled for U.S. market after study showed patients didn't benefit".

6. Arbesman M and Sheard K (2014). "Systematic review of the effectiveness of occupational therapy-related interventions for people with amyotrophic lateral sclerosis". The American Journal of Occupational Therapy. 68(1):20–6. doi:10.5014/ajot.2014.008649.

7. Associated Press (AP) News (2024). "ALS drug will be pulled from US market after study showed patients didn't benefit".

8. Bede P, Oliver D, Stodart J, van den Berg L, Simmons Z, O Brannagáin D, et al. (2011). "Palliative care in amyotrophic lateral sclerosis: A review of current international guidelines and initiatives". Journal of Neurology, Neurosurgery, and Psychiatry 82(4):413–18. doi:10.1136/jnnp.2010.232637. hdl:2262/59035.

9. Carlesi C, Pasquali L, Piazza S, Lo Gerfo A, Caldarazzo Ienco E, Alessi R, et al. (2011).

"Strategies for clinical approach to neurodegeneration in amyotrophic lateral sclerosis". Archives Italiennes de Biologie. 149(1):151–67. doi:10.4449/aib.v149i1.1267.

10. Connolly S, Galvin M, and Hardiman O (2015). "End-of-life management in patients with amyotrophic lateral sclerosis". The Lancet. Neurology. 14(4):435–42. doi:10.1016/S1474-4422(14)70221-2.

11. Dorst J, Ludolph AC, and Huebers A (2018). "Disease-modifying and symptomatic treatment of amyotrophic lateral sclerosis". Therapeutic Advances in Neurological Disorders. 11: 1756285617734734. doi:10.1177/1756285617734734.

12. Eisen A and Krieger C (2013). "Ethical considerations in the management of amyotrophic lateral sclerosis". Progress in Neurobiology 110:45–53. doi:10.1016/j.pneurobio.2013.05.001.

13. (U.S.) Food and Drug Administration (2003). "FDA approves treatment of amyotrophic lateral sclerosis associated with a mutation in the SOD1 gene" (Press release).

14. (U.S.) Food and Drug Administration, Center for Drug Evaluation and Research (2022). "FDA Approves oral Form for the treatment of adults with amyotrophic lateral sclerosis (ALS)".

15. (U.S.) Food and Drug Administration (2023). “FDA approves treatment of amyotrophic lateral sclerosis associated with a mutation in the SOD1n gene” (Press release).

16. Fymat AL (2025). “Amyotrophic lateral sclerosis: The cruel progressive neurodegenerative disease in search of a cure”, Tellwell Talent Publisher (in press).

17. Fymat AL (2025). “Amyotrophic lateral sclerosis: I. Symptomatology and staging”, Journal of Neurology and Psychology Research 6(1);1-30 (17 April 2025).

18. Fymat AL (2025). “Amyotrophic lateral sclerosis: II. Etiology and action mechanisms”, Journal of Neurology and Psychology Research 6(1);1-xx (in press).

19. Fymat AL (2025). “Amyotrophic lateral sclerosis: III. Differential diagnosis”, Journal of Neurology and Psychology Research 6(1);1-xx (in press).

20. Gordon PH (2013). "Amyotrophic lateral sclerosis: An update for 2013 clinical features, pathophysiology, management and therapeutic trials". Aging and Disease 4(5):295–310. doi:10.14336/AD.2013.0400295.

21. Hobson EV and McDermott CJ (2016). “Supportive and symptomatic management of amyotrophic lateral sclerosis”, Nature Reviews Neurology 12(9):526–38. doi:10.1038/nrneurol.2016.111.

22. Kargbo RB (2023). “Microbiome-gut-brain axis modulation: New approaches in treatment of Parkinson's disease and amyotrophic lateral sclerosis”, ACS Med. Chem. Lett. 14(7):886–8. doi: 10.1021/acsmedchemlett.3c00221.

23. Kruminis-Kaszkiel E, Juranek J, Maksymowicz W, and Wojtkiewicz J (2018). “CRISPR/Cas9 technology as an emerging tool for targeting amyotrophic lateral sclerosis (ALS)”, Int. J. Mol. Sci. 19(3). doi: 10.3390/ijms19030906.

24. Kuzma-Kozakiewicz M, Andersen PM, Ciecwierska K, Vázquez C, Helczyk O, Loose M, et al. (2019). “An observational study on quality of life and preferences to sustain life in locked-in state”, Neurology 93(10):e938-e45. doi:10.1212/WNL.0000000000008064.

25. Lewis M and Rushanan S (2007). "The role of physical therapy and occupational therapy in the treatment of amyotrophic lateral sclerosis". NeuroRehabilitation 22(6):451–61. doi:10.3233/NRE-2007-22608.

26. Lui AJ and Byl NN (2009). "A systematic review of the effect of moderate intensity exercise on function and disease progression in

amyotrophic lateral sclerosis". Journal of Neurologic Physical Therapy 33 (2): 68–87. doi:10.1097/NPT.0b013e31819912d0.

27. Macpherson CE and Bassile CC (2016). "Pulmonary physical therapy techniques to enhance survival in amyotrophic lateral sclerosis: A systematic review". Journal of Neurologic Physical Therapy 40(3):165–75. doi:10.1097/NPT.0000000000000136.

28. Majmudar S, Wu J, and Paganoni S (2014). "Rehabilitation in amyotrophic lateral sclerosis: why it matters". Muscle & Nerve 50(1):4–13. doi:10.1002/mus.24202.

29. Miller RG, Mitchell JD, and Moore DH (2012). "Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)". The Cochrane Database of Systematic Reviews 2012(3): CD001447. doi:10.1002/14651858.CD001447.pub3.

30. Mora JS (2017). "Edaravone for treatment of early-stage ALS", The Lancet Neurology 16(10): 772. doi:10.1016/S1474-4422(17)30289-2.

31. O'Brien D, Stavroulakis T, Baxter S, Norman P, Bianchi S, Elliott M, et al. (2019). "The optimization of noninvasive ventilation in amyotrophic lateral sclerosis: A systematic review". The European Respiratory Journal 54 (3):1900261. doi:10.1183/13993003.00261-2019.

32. Orrell RW (2010). "Motor neuron disease: Systematic reviews of treatment for ALS and SMA". British Medical Bulletin 93:145–59. doi:10.1093/bmb/ldp049.

33. Paganoni S, Karam C, Joyce N, Bedlack R, and Carter GT (2015). "Comprehensive rehabilitative care across the spectrum of amyotrophic lateral sclerosis". NeuroRehabilitation 37(1):53–68. doi:10.3233/NRE-151240.

34. Pinto S and Carvalho M (2014). "Breathing new life into treatment advances for respiratory failure in amyotrophic lateral sclerosis patients". Neurodegenerative Disease Management 4(1):83–102. doi:10.2217/nmt.13.74.

35. Radunovic A, Annane D, Rafiq MK, Brassington R, and Mustfa N (2017). "Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease". The Cochrane Database of Systematic Reviews 10(10):CD004427. doi:10.1002/14651858.CD004427.pub4.

36. Sauvé WM (2016). "Recognizing and treating pseudobulbar affect". CNS Spectrums 21(S1):34–44. doi:10.1017/S1092852916000791.

37. Soriani MH and Desnuelle C (2017). "Care management in amyotrophic lateral sclerosis". Revue Neurologique 173(5):288–99. doi:10.1016/j.neurol.2017.03.031.

38. Sulistyo A, Abrahao A, Freitas ME, Ritsma B, and Zinman L (2023). "Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease". The Cochrane Database of Systematic Reviews 2023(8):CD004030. doi:10.1002/14651858.CD004030.pub4.

39. Takei K, Watanabe K, Yuki S, Akimoto M, Sakata T, and Palumbo J (2017). "Edavarone and its clinical development for amyotrophic lateral sclerosis", Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration 18 (sup1):5–10. doi:10.1080/21678421.2017.1353101.

40. Vucic S and Kiernan MC (2013). "Utility of transcranial magnetic stimulation in delineating amyotrophic lateral sclerosis pathophysiology", Handb. Clin. Neurol. 116:561–75. doi: 10.1016/B978-0-444-53497-2.00045-0.

41. Vucic S, Ziemann U, Eisen A, Hallett M, and Kiernan MC (2013). "Transcranial magnetic stimulation and amyotrophic lateral sclerosis: Pathophysiological insights", J.

Neurol. Neurosurg. Psychiatry 84(10):1161–70. doi: 10.1136/jnnp-2012-304019.

42. White JA, Banerjee R, and Gunawardena S (2016). “Axonal transport and neurodegeneration: How marine drugs can e used for the development of therapeutics”, Marine Drugs 14(5): 102. doi:10.3390/md14050102.

43. Wicks P (2014). "The ALS ice bucket challenge – can a splash of water reinvigorate a field?". Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration 15(7–8):479–80. doi:10.3109/21678421.2014.984725.

44. Wong C, Stavrou M, Elliott E, Gregory JM, Leigh N, Pinto AA, et al. (2021). "Clinical trials in amyotrophic lateral sclerosis: a systematic review and perspective". Brain Communications 3(4): fcab242. doi:10.1093/braincomms/fcab242.