TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rare degenerative disorder of motor neurons of the cerebral cortex, brain stem, and spinal cord resulting in progressive wasting and paralysis of voluntary muscles (1). The worldwide incidence of ALS is currently approximately 2/100,000/year (2) and may be increasing (3), with a lifetime risk of 1 in 600 to 1 in 1000. Fifty percent of ALS patients die within three years of onset of symptoms and 90% die within five years (4). The median age of onset is 55 years with a slight male predominance (3:2 male to female ratio). The cause in most cases is unknown. Age and gender are the only risk factors repeatedly documented in epidemiological studies (5). No treatment prevents or reverses the disease (6). Many causes of ALS have been proposed including toxicity from excess excitation of the motor neuron by transmitters such as glutamate (7), free radical-mediated oxidative cytotoxicity (8), neuroinflammation (9), mitochondrial dysfunction 10), specific genetic mutations including SOD1 and C9orf72 (11), autoimmune processes (12), cytoskeletal abnormalities (13), aberrant activation of cyclooxygenase (14), and hyperexcitability of both peripheral motor nerve axons (15) and cortical motor neurons (7).

ALS presents with motor symptoms including weakness, muscle atrophy, spasticity, and fasciculations, typically sparing sensation, bladder function, and extraocular muscles (16). Regions of the body vary at presentation with the majority presenting with limb onset and a minority (about 20%), frequently older women, demonstrating bulbar dysfunction as the initial sign. However, the disease in all patients involves a combination of upper motor neuron (UMN) and lower motor neuron (LMN) symptoms progressing from one of four body segments (craniobulbar, cervical, thoracic, and lumbosacral) to the next. UMN findings including spasticity, increased muscle tone resistant to stretching and passive range of motion, incoordination of limbs, and increased deep tendon reflexes as well as pathologic reflexes including positive Babinski, Hoffman, cross adductor, and snout and exaggerated jaw jerk reflexes, depending on the site of involvement. Some patients, especially those with bulbar involvement, exhibit pseudobulbar affect (PBA, also known as emotional incontinence) manifested by outbursts of crying or laughter inconsistent with the patient's mood. PBA is though to be due to loss of cortical inhibition to the part of the brainstem controlling these emotional displays by degeneration of bilateral corticobulbar tracts or loss of corticocerebellar inhibition to this part of the brain (17). LMN symptoms include weakness, atrophy, muscle fasciculations and cramps, and depressed deep tendon reflexes. Patients with substantial neck extensor weakness, not uncommon in ALS, may present with dropped head syndrome. Patients with bulbar weakness usually present with dysphagia and flaccid dysarthria, slurring of the speech with a nasal quality, as well as excessive salivation, also known as sialorrhea. Fasciculations may be a challenge to see on examination in obese or older patients and in the tongue due to difficulty relaxing the latter muscles. Weakness of the diaphragm and intercostal muscles is associated with dyspnea that is characteristically most prominent when the patient lies supine and often seen early with sleep-disordered breathing.

About 10% of patients also present with frontotemporal dementia (FTD), with up to nearly 50% demonstrating behavioral changes or loss of executive or language function without meeting criteria for dementia at presentation. The incidence of frontotemporal dementia is greater in patients with some forms of familial ALS, especially those associated with mutations in the genes for C9orf72, FUS, TDP-43, and VCP (18). A minority of patients also report sensory symptoms such as distal paresthesias, usually in the absence of sensory findings on examination. Typically Onuf's nucleus of the bladder and cranial nerve nuclei innervating the extraocular muscles are spared, though some patients report urinary urgency and rarely double vision late in the course of the disease (16).

THE MANAGEMENT OF ALS

Multidisciplinary care

The care of ALS patients is best carried out in a multidisciplinary clinic where personnel with specific expertise can evaluate and assist the patient in regard to the complications and symptomatic management of the disease. These include neurologists, rehabilitation medicine specialists, pulmonologists, respiratory, physical,

occupational, and speech therapists, social workers, psychologists, and palliative medicine specialists. Multidisciplinary management of ALS has been shown to benefit patients and families in regard to quality of life and has recently also been demonstrated to improve survival (19). In 2013, the American Academy of Neurology (AAN) approved quality measures regarding the management of ALS (20), recommending that an ALS multidisciplinary care plan be developed as a measure and updated at least once annually (Table 1).

Cognitive impairment

FTD often significantly increases the level of care required, interfering with the patients' ability to make informed decisions about medical care and rendering communication with other family members as well as physicians challenging at times (21). Assessment for cognitive impairment at clinic visits, such as the employment of the ALS-Cognitive Behavioral Screen (ALSCBS) (22), should occur periodically, especially if family members express concerns about changes in behavior or decision-making. If suspicion for FTD is high, formal neuropsychological evaluation or an evaluation by a dementia specialist may be of value. The 2013 AAN quality measures suggests that screening for cognitive and behavioral impairment using tools like the ALSCBS should be performed at least once annually (20).

Declining Mobility

As an ALS patient develops progressive weakness in the lower extremities, typically, the ability to ambulate unassisted becomes increasingly impaired. Bracing such as ankle foot orthotics may increase gait stability for a prolonged period. However, as patients become more prone to falling, evaluation by physical therapy is imperative to determine the need for assistive devices such as a walker or power wheelchair. The 2013 AAN quality measures specify that screening for falls is recommended at least annually to prevent traumatic injury (21).

Dysarthria

Dysarthria in ALS is difficult to treat. Conventional articulation training is ineffective; however, some adaptive strategies taught by a speech-language therapist may be useful (23). These include slowing the speech rate, increasing the precision of speech production, and decreasing background noise. As the disease progresses, various communicative aids may play an ever increasing role. Communication through an alphabet or word board works well early on when patients still have reasonable arm function. Binary command and yes/no systems using eye gaze can be particularly useful for a patient in the later stages of the disease. The Speakit! application for the iPad or computer may suffice for some time and be an affordable alternative to a more expensive augmentative and alternative communication (AAC) device. Caregivers of patients report that AAC devices are helpful to stay connected, respond to patients' needs, and discuss complex important issues, including medical information (24). As emphasized by the 2013 AAN quality measures, dysarthric patients should be offered a referral at least once annually to a speech-language pathologist for an augmentative/alternative communication evaluation (21).

Dysphagia

Dysphagia is denoted in ALS patients by difficulty chewing and swallowing, nasal regurgitation, or coughing when drinking liquids (25). A speech-language pathologist and nutritionist should be consulted early for clinical swallowing evaluations and recommendations on dietary modifications, respectively. Clinical signs and symptoms of dysarthria and dysphagia in ALS often occur simultaneously. Dietary modifications include thickening liquids and preparing food that forms easily into a bolus. A modified barium swallow is generally only needed when a patient has a history of having more difficulty with solids as opposed to liquids. These examinations are useful not only for accurately determining the presence of aspiration but also for providing a guide as to which textures of food are safe for the patient. With marked dysphagia or in patients who become malnourished due to hypermetabolism induced by the disease itself, percutaneous gastrostomy (PEG) tube placement should be performed. PEG tube placement should also be considered prophylactically in ALS patients with respiratory compromise and a forced vital capacity of less than or equal to 50% of normal, as respiratory complications are generally considered unacceptably high beyond this degree of involvement. The 2013 AAN quality measures indicate that ALS screening for dysphagia, weight loss, and impaired nutrition should occur at least every 3 months (21).

Respiratory compromise

ALS patients typically die from their disease as a consequence of progressive involvement of respiratory muscles. Initially, patients experience symptoms that are a consequence of nocturnal hypercapnia, including morning headaches and vivid dreams (26). They later report other symptoms including dyspnea on exertion or the need to take a breath while talking and eventually an inability to lie flat. Symptomatic respiratory involvement correlates best with forced vital capacity (FVC), usually occurring when the FVC falls bellow 50% of normal (26). Bi-level

positive airway pressure (BiPAP) can alleviate many of the symptoms of respiratory compromise such as dyspnea and fatigue but only for a limited time. There is also evidence it may prolong survival in patients who tolerate it well, by a number of months (27). Tracheostomy and mechanical ventilation is a more permanent alternative but is costly and requires considerable willingness on the part of family. Additionally, it does not alter the course of the disease, which will continue to cause more weakness to the point where the patient is unable to move at all and locked in. Usually the decision to proceed with tracheostomy and mechanical ventilation is best made in discussion with a pulmonologist. The 2013 AAN quality measures specify that pulmonary function studies should be obtained from patients every three months to determine eligibility for noninvasive ventilation and treatment options for respiratory insufficiency discussed at least annually (21).

Reactive depression

Reactive clinical depression is common in ALS, occurring in 9 to 11% of patients (28). A supportive surrounding that includes close family, social, and religious support systems, and participation in support groups are all helpful for patients dealing with depression. Once the diagnosis is confirmed, the patient should be counseled regarding the prognosis. Antidepressant medication, including tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin- norepinephrine reuptake inhibitors, may assist with mood elevation, appetite stimulation, and sleep, and should be offered to every patient. In addition to their antidepressant effects, tricyclic medications may also reduce oral secretions and drooling due to their anticholinergic properties. Referral to a psychiatrist or clinical psychologist or palliative medicine specialist may be warranted. Counseling should also be offered to depressed spouses and other family members (29).

Other ALS-Related Symptoms

Spasticity

Spasticity is common in ALS and can significantly impair mobility and other activities of daily living. Baclofen, a □–aminobutyric acid (GABA) agonist, facilitates spinal motor neuron inhibition and is typically the first-line medication. Baclofen is gradually escalated as necessary but many patients cannot tolerate higher doses of the medication (over 120 mg a day) due to increased weakness, fatigue, and sedation. Tizanidine, an alpha 2-agonist, has also been effective in spasticity management. Its mechanism of action is believed to be through the inhibition of excitatory interneurons. Tizanidine has a similar side effect profile as baclofen. Benzodiazepines such as diazepam can be used for spasticity but can cause respiratory depression and somnolence. If patients continue to have a significant amount of spasticity, especially of the lower extremities, an intrathecal baclofen pump may also be useful in reducing spasticity and pain (30).

Muscle cramps

Muscle cramps are common in ALS, poorly responsive to treatment, and often debilitating. They are thought to occur as a consequence of peripheral axonal hyperexcitability resulting from regenerating nerve axons. There have been a number of randomized treatment trials addressing this frequently disabling symptom but most have been unsuccessful (31). Anecdotally, quinine sulfate taken orally may be helpful for symptomatic relief of muscle cramps, though the drug is no longer available in the United States due to safety issues. Recently, the cardiac antiarrhythmic medication mexiletine has been demonstrated to reduce the frequency and severity of muscle cramps in ALS in a dose dependent manner (32). In addition to medication, a daily stretching program can be helpful.

Sialorrhea

Excessive secretions become a concern to patients typically in parallel with bulbar dysfunction and can sometimes lead to aspiration (23). Medications with strong anticholinergic effects, including some of the tricyclic antidepressants and glycopyrrolate can be effective at drying up secretions. Transdermal scopolamine patches may also be effective in this setting. Botulinum toxin injections into the salivary glands can be effective in some patients (33). Radiation targeting the salivary glands is another option for refractory sialorrhea that may be helpful but can often cause complications (34).

Pseudobulbar affect

Pseudobulbar affect (PBA) is more common in the bulbar form of ALS, though recent literature suggests it can occur in up to a third of ALS patients overall (35). Combined use of dextromethorphan and quinidine (30 mg of each drug) was found to reduce pseudobulbar affect in a multicenter trial in which primary outcomes were a change from baseline on the Center for Neurologic Study–Lability Scale, decrease in laughing/crying episode

rates, and improvement in quality of life (36). This drug is now available as Nuedexta and taken one tablet twice daily. Selective serotonin reuptake inhibitor (SSRI) medications may also be helpful though they have not been studied in the ALS population in a randomized fashion.

Per the 2013 AAN quality measures, ALS symptomatic therapy should be offered for pseudobulbar affect, sialorrhea, muscle cramps, and other ALS-related symptoms as they arise (21).

End-of-life decision making and palliative and hospice care

Although ALS is a fatal condition, it may take many years before a patient who has ALS succumbs to its effects. Poor prognostic factors include older age at onset of symptoms, early bulbar or pulmonary dysfunction, short duration from symptom onset to diagnosis, and predominance of LMN findings at the time of diagnosis (37). The expected survival rates may vary depending on the patient's decision regarding the use of mechanical ventilation and feeding tubes, but the overall survival rate remains low. ALS patients may have a great deal of time to think of their impending death and also the various decisions they need to make at different stages of their disease. As the 2013 AAN quality measures indicate, ALS patients should be offered assistance in planning for end of life issues, such as consultation with a palliative medicine specialist, the drafting of an advance directive, or the initiation of hospice care, at least once annually (21).

DISEASE MODIFYING THERAPY

Riluzole

For more than twenty years, riluzole has remained the only FDA approved medication proven to slow the progression of ALS. Pharmacological mechanisms of riluzole include interference with NMDA-receptor mediated responses, stabilization of the inactivated state of voltage-dependent sodium channels, inhibition of glutamate release from synaptic terminals, and activation of extracellular glutamate uptake. A recent Cochrane Database Review concluded that riluzole 100 mg daily prolongs median survival by about two to three months based on analysis of four randomized controlled trials (38). The drug is generally well-tolerated with asthenia, nausea, and an increase in serum alanine aminotransferase the most common side effects (39). Liver function should be monitored periodically during therapy. The 2013 AAN quality measures indicate that the use of any disease modifying therapy in ALS, including riluzole, be discussed at least once annually (21).

Previous trials of disease modifying therapies and future directions

Numerous therapeutics have been studied in ALS without success (40). Since riluzole became available, there have been a number of other therapies aimed at targeting motor neuronal excitotoxicity including xaliproden, topirimate, lamotrigine, gabapentin, memantine, and talapanel. Stabilization or repair of impaired mitochondrial function using the drugs minocycline, coenzyme Q10, and creatine did not effect disease progression or survival. A number of nerve growth factors have been studies in the last few years without showing benefit including BDNF, NTF, CNF, and IGF-1. Targeting of neuroinflammation with cyclophosphamide, azathioprine, prednisone, pioglitazone, minocycline, and whole lymphoid irradiation with bone marrow transplantation has not proven fruitful. Diaphragmatic pacing to treat respiratory failure has been shown in two large multicenter studies to accelerate the disease (41,42). Ceftriaxone, which increases expression of the glutamate transporter EAT2 on astrocytes to reduce concentrations of free glutamate contributing to excitotoxicity, was recently shown in a phase III trial to have no impact on the disease (43). While dexpramipexole was shown to slow progression in a phase II study, a larger multicenter phase III trial was unsuccessful (44).

Current or recently completed trials have addressed novel pathogenic mechanisms in ALS including corticomotor neuronal and peripheral axonal hyperexcitability (mexiletine and retigabine) and microglial activation (gilenya and tocilizumab). Additionally, a trial of Nuedexta was recently completed, showing improvement of bulbar function in ALS (45). In familial ALS with SOD1 mutations, a recent study of antisense oligonucleotide therapy delivered intrathecally to patients showed that the treatment was safe and tolerable though it was not empowered to demonstrate efficacy (46). Finally, a number of stem cell studies are underway or in different stages of development, most notably an open label study of fetal stem cells injected into the spinal cords of patients that was proven safe and tolerable (47). Though there have been many treatment trials in the last few decades that have failed, these recent or current studies have redirected the focus to selective targeting of unique causes of the disease not previously considered and hold out hope to patients suffering from this terrible and relentless disease.

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Table 1. American Academy of Neurology-approved quality measures of ALS (20).

1. ALS multidisciplinary plan developed or updated at least annually.
2. Disease modifying pharmacotherapy (riluzole) for ALS discussed annually.
3. ALS cognitive and behavioral impairment screening performed at least annually for cognitive impairment (frontotemporal dementia screening and Cognitive Behavioral Screen, i.e. ALS CBS).
4. ALS symptomatic treatment offered for sialorrhea, pseudobulbar affect, and other ALS symptoms.
5. ALS respiratory insufficiency querying and referral for pulmonary function testing, performed at least every 3 months.
6. ALS non-invasive ventilation treatment for respiratory insufficiency or cough assist discussed at least annually.
7. ALS screening for dysphagia, weight loss, and impaired nutrition performed at least every 3 months
8. ALS nutritional support, including dietary or enteral nutrition with percutaneous endoscopic or radiographic inserted gastrostomy tube placement, offered at least annually.
9. ALS communication support referral offered at least annually for patients with dysarthria to a speech language pathologist for an augmentative/alternative communication evaluation.
10. ALS end of planning assistance (advance directives, hospice placement, invasive ventilation) offered at least annually.
11. ALS falls query performed within the previous 12 months.

Table 2. Medications commonly used for symptom management in ALS.

Symptom	Medication	Starting Dose	Dose adjustment	Side Effects	Monitoring
Spasticity	Baclofen	5 mg three times a day	Increase by 15 mg a day every three days (maximum usually 80-100 mg total daily dose)	Sedation, dizziness, respiratory depression, ataxia, seizures, weakness	Cr at baseline
	Tizanidine	2 mg every 6-8 hours	Increase by 2-4 mg every 1-4 days (maximum 36 mg total daily)	Hepatotoxicity, bradycardia, hypotension, hallucinations, Stevens-Johnson reaction, dizziness, somnolence, vomiting	LFTs monthly
	Diazepam	5 mg two to three times a day	Increase by 5 mg every 1-4 days (maximum 30 mg a day)	Respiratory depression, seizures, suicidality, bradycardia, hypotension	LFTs
Muscle cramps	Quinine sulfate (currently not recommended by FDA)	300 mg at night		Hemolytic-uremic syndrome,thrombo-cytopenic purpura, cinchonism, Stevens Johnson reaction, bronchospasm, arrythmias, headache, dizziness	CBC, LFTs
	Mexiletine	150 mg twice daily	Increase by 150 mg weekly (maximum 600 mg a day)	Nausea, tremor, dizziness, arrthymias	BMP, ECG a month after initiating treatment
Sialorrhea	Amitriptyline	10 mg at bedtime	Increase weekly by 10 mg up to 75 mg daily	Hypotension, hypertension, suicidality, syncope, arrythmias, sedation, dry mouth, urinary retention	ECG if known cardiac disease
	Glycopyrrolate	1 mg two or three times daily	Increase by 1-2 mg every 3-4 days (maximum 8 mg/day)	Hypersensitivity, anaphylaxis, seizures, arrhythmias, dry mouth, vomiting, urinary retention	
Pseudo-bulbar affect	Nuedexta	One capsule twice a day		Infusion reaction, anaphylaxis, myelosupression, infection, cardiac dysrhythmia	BMP, ECG at baseline and 4 hours after first dose if at risk of prolonged QT
Depression	Nortriptyline	25 mg at bedtime	Increase every 3 days by 25 mg (maximum 150 mg/day)	Hypotension, hypertension, suicidality, syncope, arrythmias, sedation, dry mouth, urinary retention	ECG if known cardiac disease; symptoms of suicidality
	Sertaline	50 mg daily	Increase every week by 25-50 mg (maximum 200 mg/day)	Suicidality, seizures, hyponatremia, nausea, headache, sedation, insomnia	Symptoms of suicidality
	Duloxetine	30 mg daily	Increase every week by 30 mg (maximum 120 mg/day)	Suicidality, seizures, hyponatremia, syncope, nausea, headache, sedation, insomnia, decreased appetite	Cr at baseline; symptoms of suicidality

CBC: complete blood count; Cr: creatinine; ECG: electrocardiogram; BMP: basic metabolic profile; LFT: liver function test