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Review Article

Amyotrophic Lateral Sclerosis: An update for 2013 Clinical Features, Pathophysiology, Management and Therapeutic Trials

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ABSTRACT: Amyotrophic lateral sclerosis (ALS), first described by Jean-Martin Charcot in the 1870s, is an age-related disorder that leads to degeneration of motor neurons. The disease begins focally in the central nervous system and then spreads relentlessly. The clinical diagnosis, defined by progressive signs and symptoms of upper and lower motor neuron dysfunction, is confirmed by electromyography. Additional testing excludes other conditions. The disease is heterogeneous, but most patients die of respiratory muscle weakness less than 3 years from symptom-onset. Like other age-related neurodegenerative diseases, ALS has genetic and environmental triggers. Of the five to 10% of cases that are inherited, mutations have been discovered for a high proportion. In addition to genetic factors, age, tobacco use, and athleticism may contribute to sporadic ALS, but important etiologies are unidentified for most patients. Complex pathophysiological processes, including mitochondrial dysfunction, aggregation of misfolded protein, oxidative stress, excitotoxicity, inflammation and apoptosis, involve both motor neurons and surrounding glial cells. There is clinical and pathological overlap with other neurodegenerative diseases, particularly frontotemporal dementia. The mechanisms leading to disease propagation in the brain are a current focus of research. To date, one medication, riluzole, licensed in 1996, has been proved to prolong survival in ALS. Numerous clinical trials have so far been unable to identify another neuroprotective agent. Researchers now aim to slow disease progression by targeting known pathophysiological pathways or genetic defects. Current approaches are directed at muscle proteins such as Nogo, energetic balance, cell replacement, and abnormal gene products resulting from mutations. Until better understanding of the causes and mechanisms underlying progression lead to more robust neuroprotective agents, symptomatic therapies can extend life and improve quality of life. Palliative care programs such as hospice give emotional and physical support to patients and families throughout much of the disease course.

Key words: amyotrophic lateral sclerosis, neurodegeneration, epidemiology, pathophysiology, diagnosis, treatment

Amyotrophic Lateral Sclerosis (ALS) is characterized by progressive degeneration of upper (UMN) and lower (LMN) motor neurons in the brain and spinal cord. It is the most common motor neuron disease (MND), which includes primary lateral sclerosis, a disease restricted to UMNs that makes up 1-3% of MND, and progressive muscular atrophy, limited to LMNs, which is responsible for approximately 10% of MND [1]. Predominance of UMN features probably carries a better prognosis, even for patients with ALS [2]. Incidence rates for ALS range from 1.2-4.0 per 100,000 person-years in Caucasians [3-6]. The rate may be lower in some ethnic populations including American Indians [7], and, historically, as much as 50 times higher in Guam, Japan's Kii Peninsula, and western New Guinea [8]. Incidence rates increase with

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age, peaking between 70 and 80 years, and are higher in men than women [9,10].

ALS begins in limb or bulbar muscles and then spreads to contiguous, and eventually respiratory, myotomes. Survival ranges from months to decades, but is usually less than three years from when symptoms first appear [11].

Jean-Martin Charcot, employing the clinicoanatomic method that he devised, described the clinical and pathological features of ALS during a series of lectures in the 1860s and 1870s [12]. The methodology available to Charcot was primitive by contemporary standards, but his approach was so insightful that his original descriptions are considered accurate today. Sir William Gowers and Lord Russell Brain made major contributions in the United Kingdom, using the label MND instead of ALS because they believed that all patients have pathology of both UMNs and LMNs, either during life or at autopsy. The paucity of American neurologists early in the 20th Century meant that the illness was largely overlooked in the New World until 1939 when Lou Gehrig, the notable first baseman for the New York Yankees, contracted ALS. Gehrig, nicknamed the "iron horse" for playing 2130 consecutive games over 14 years, first exhibited signs in 1938; he finished the season but with a batting average 45 points below his career average [13,14]. By April 1939, he was no longer able to play and removed himself from the lineup. Gehrig died two years later, having participating in an early clinical trial [15]. Gehrig's name is still used as an eponym for ALS in the United States; MND is used in the U.K., whereas SLA (sclérose latérale amyotrophique), the term Charcot gave the disease, is preferred in France.

While ALS is nearly as mysterious today as it was in the first part of the 20th Century, recent breakthroughs in understanding familial forms (fALS) have led to new hypotheses for disease triggers and mechanisms of propagation. Known mutations now account for much of the rare instances of inherited ALS. Sporadic ALS (sALS) is thought to have both genetic and environmental influences, but the principal causes await discovery. Once the disease begins, a number of processes transpire in both neurons and surrounding glial cells; how these mechanisms interact is an area of active research [16]. As in other neurodegenerative diseases, a prominent event in damaged neurons is aggregation of misfolded protein, which might influence nearby wild type protein to change conformation, and in this way, explain how a disease that begins in one area is transmitted widely in the brain [17]. Defects in RNA processing might also contribute to disease propagation, which could occur by local spread, through neuronal networks or by affecting populations of cells rendered vulnerable by developmental errors [18].

The lethal prognosis and absence of treatments for ALS mean that all care is palliative. One medication, riluzole, approved for use in 1996, slows deterioration by approximately two months, but 17 years and numerous trials later, no treatment can halt the course of the disease. Multi-disciplinary clinics [19] and non-invasive ventilation for those with respiratory failure also appear to ameliorate the outcome modestly. Clinical trials currently test medications aimed to interfere with a known cellular event and slow the disease course; participation in research conveys hope to patients and may also improve survival time [20].

This review summarizes the clinical manifestations, disease mechanisms, approaches to care and design of trials for ALS, giving an overview of the current understanding of the disease, and concludes with a section on future directions.

CLINICAL FEATURES AND DIAGNOSIS

ALS leads to progressive degeneration of the motor neurons that supply voluntary muscles, including LMNs in the medulla and anterior horn of the spinal cord as well as UMNs in the cerebral cortex. The effect clinically is progressive muscle weakness leading to death, usually from respiratory failure. Median survival ranges from months to decades but is 19 months from diagnosis and 30 months from onset on average [11,21]. The variability and overall rapid progression make it difficult to predict survival time or the timing of interventions. In general, limb-onset, younger age, better motor function, higher breathing capacity, stable weight, and longer interval between symptom onset and diagnosis are associated with longer survival [22].

Loss of LMNs causes fasciculation, cramps, muscle atrophy and marked weakness, which is often more disabling for patients than the spasticity, hyperreflexia and modest weakness associated with UMN disease. Babinski and Hoffmann signs, along with emotional lability are also characteristic findings of UMN degeneration.

ALS is clinically heterogeneous even among family members harboring the same gene mutation; a single etiology can lead to numerous clinical syndromes. In addition to variable progression rate, UMN and LMNs are differentially affected, onset occurs in different body regions, and cognitive as well as behavioral disturbances vary.

ALS begins in the limbs, usually the arms, in about two-thirds of patients. The first symptoms are most often unilateral and focal. Early findings include foot drop, difficulty walking, loss of hand dexterity or weakness when lifting the arms. As limb function deteriorates, patients become dependent on caregivers. They may fall

and lose the ability to walk. Bulbar-onset ALS, which is more frequent in older women, carries a worse prognosis [23]. The first symptom is often dysarthria followed by dysphagia, which may progress to sialorrhea, malnutrition and anarthria. An atrophied fasciculating tongue is practically diagnostic of bulbar ALS. Axial weakness can cause dropped head and kyphosis, which are associated with pain and poor balance. Sphincter and sensory functions are usually, but not always, spared. Eye movements are preserved until advanced stages.

Cognitive impairment in ALS was described by Pierre Marie in the 19th century [24], but was considered uncommon until recently. Overt frontotemporal dementia (FTD) occurs in approximately 15% of people with ALS, but up to 50% are classified as impaired if measured by neuropsychological tests [25,26]. Primary progressive aphasia, semantic dementia and the behavioral variant are subtypes of FTD that affect executive function, language, judgment, personality, and behavior. Patients with ALS and dementia have shorter survival, possibly as a result of indecisiveness about care [27].

Depression and anxiety can occur during any stage of the disease, from time of diagnosis to respiratory failure, but patients with ALS often approach the disease philosophically and rates of depression seem to be lower than expected [28]. When present, emotional symptoms impair quality of life through poor sleep and appetite, as well as feelings of hopelessness [29].

Pain can occasionally result from involvement of sensory neurons, and frequently from contractures, immobility, inability to turn in bed, or bedsores. The suffering that arises from being unable to move can be intense (www.nybooks.com/articles/archives/2010/jan/14/night).

Morning headache, weak cough, orthopnea, and exertional dyspnea are early respiratory symptoms. As the disease advances, shortness of breath occurs during simple tasks such as dressing and eating, and eventually at rest.

The diagnosis, which depends on progressive UNM and LMN findings by history and examination, is accurate 95% of the time when made by an experienced clinician [30]. Electromyography confirms widespread LMN disease and excludes other diseases such as multifocal motor neuropathy with conduction block. Brain and spinal MRI rule out conditions that affect the UMN, including cervical spondylosis. Occasionally the brain MRI shows bilateral signal changes within the corticospinal tracts, a finding that is pathognomonic of ALS.

The El Escorial criteria help standardize diagnosis for clinical research studies [31] (Table 1). Progressive LMN disease by clinical and electromyographic examination, and clinical UMN signs are the core. Patients are classified by the number of involved body regions: bulbar, cervical, thoracic or lumbosacral. Recent modifications created on Awaji Island near Japan may improve diagnostic sensitivity, particularly for those with bulbar-onset in whom limb findings can be subtle [32].

Table 1. Summary of Revised El Escorial Diagnostic Criteria for ALS [31]

Clinically possible ALS	UMN and LMN sings in one region, or UMN signs in at least two regions, or UMN and LMN signs in two regions with no UMN signs rostral to LMN signs
Laboratory-supported probable ALS	UMN signs in one or more regions and LMN signs defined by EMG in a least two regions
Clinically probable ALS	UMN and LMN signs in two regions with some UMN signs rostral to the LMN signs
Clinically definite ALS	UMN and LMN signs in three regions

EMG – electromyogram; LMN- lower motor neuron; UMN – upper motor neuron

PATHOGENESIS

More than a century after Charcot described ALS, the etiologies are undiscovered for most patients, but genetic discoveries have recently improved understanding of fALS. Approximately 5-10% of ALS is inherited, with responsible mutations identified in nearly 60%.

Among the genes reported in ALS pedigrees, there is strong evidence supporting a pathogenic role for the Cu / Zn superoxide dismutase 1 (SOD1), transactive response DNA-binding protein of 43 kD (TARDBP), fused in sarcoma (FUS) and c9ORF72 genes [33]. Other genes possibly implicated in fALS include the angiogenin, ataxin-2, optineurin, profiling 1, ubiquilin-2, valosin containing protein (VCP) and VAMP-associated protein type B (VAPB) genes [34].

A single mutation can lead to different clinical presentations, suggesting that varying mechanisms influence outcome, and similar ALS phenotypes result from different mutations, implying that ALS is a syndrome of different causes that share like pathophysiological pathways [18].

Gene mutations cause motor neuron death through different pathways: SOD1 mutations lead to oxidative stress; TARDBP, FUS and c9ORF72 induce disturbances in RNA machinery; VAPB affects endosomal vesicle trafficking; and UBQLN2 contributes to ubiquitination.

The first mutation discovered was in the SOD1 gene on chromosome 21 [35]. The SOD1 mutation was used to create a transgenic animal model that has been used to screen new drugs and study disease physiology. Currently, 15–20% of fALS cases, inherited mostly in an autosomal dominant pattern, are due to one of more than 160 mutations that affect five exons and some introns of the gene. Five percent of patients with sALS carry similar mutations. SOD1 mutations are associated with deposition of ubiquitinated TDP-43 negative SOD1 protein in neurons [36]. SOD1 appears to trigger disease in motor neurons, but astrocytes and microglia promote disease progression, perhaps through mishandling of glutamate [37]. Clinical characteristics of families harboring SOD1 mutations include young age-of-onset, onset in the leg with predominance of LMN features, and low frequency of cognitive disturbances. Disease duration spans an average of 9 months (A4V mutation) to decades (D90A mutation) [38].

TARDBP mutations account for about 5% of FALS [39]. Nearly 50 mutations have been identified, mostly involving the C-terminal glycine-rich region of the protein. Similar to sALS, mutations in the TARDBP gene cause TDP-43 positive inclusions in the brain, which, along with FUS+ aggregates, may lead to defects in RNA processing. Caucasians with ALS linked to TARDBP mutations typically have onset in the arm while people of Asian descent have bulbar onset [40], longer disease duration and infrequent cognitive disturbances [33].

Mutations in the FUS gene account for about 5% of FALS and less than 1% SALS. More than 50 mutations have been identified, most affecting the last 17 amino acids of the protein, the commonest being Arg521Cys [41]. All except one mutation is dominant [42]. FUS positive TDP negative inclusions are found pathologically. FUS mutations cause ALS with age-of-onset younger than 40 years in one-third of cases, usual onset in the arm, and survival of less than two years [33].

The c9ORF72 gene is now thought to be the most frequent cause of genetic ALS. A hexanucleotide repeat in the gene accounts for up to 40% of fALS and 7% of sALS [43]. Mutations in the c9ORF72 gene cause FTD or ALS that are marked by TDP-43 protein accumulation in the brain along with deposits of p62 [44]. C9ORF72 mutations are also linked to other neurological diseases [45].

There are a few leads for the causes of sALS. An elevated estimate of heritability in twin studies [46]; gender predominance depending on phenotype [47]; and familial aggregation of neurodegenerative disorders [48,49] suggest genetic factors at play. Genome-wide association studies (GWAS) have been used to search for susceptibility factors that promote motor neuron death in patients with sALS, yielding few successes so far. Abnormal SMN1 copy number is one such risk gene [50]. Other associations, including the DPP6 and VEGF genes, could not be identified by independent researchers or were found only in certain geographic regions [51-55]. GWAS are a difficult undertaking in ALS because sample sizes must be very large to detect small genetic effects [41].

Advancing age and exposure to tobacco smoke are associated with sALS [56], but there is currently little evidence to support the contribution of other environmental risk factors [1,56-60]. A pooled analysis of five large cohorts found modest but significant associations with active smoking, former smoking, duration of smoking, and quantity of cigarettes [61]. Other possible associations include athleticism [62], particularly professional sports, pesticide exposure [63], and service in the first Gulf war [64]. A study in Italy from 1970-2001 found a 6.5 times higher risk in soccer players than non-players [65]. Trauma is a possible contributor to all neurodegenerative diseases [66]. Associations with electrical fields, viral infection and various toxins are uncorroborated [67,68].

Pathophysiological mechanisms that contribute to cell death after disease-onset include mitochondrial dysfunction, protein aggregation, generation of free radicals, excitotoxicity, disrupted axonal transport, inflammation, and apoptosis [69]. Levels of Nogo-A, a protein that inhibits regrowth of axons, are increased in the muscle of patients and transgenic mice, suggesting that muscle function could influence the health of motor neurons [70,71]. Cell death may occur, at least in SOD1 ALS, by non-cell autonomous mechanisms in which surrounding support cells are required [72].

There is now evidence that pathological protein aggregates in the brain are actively disseminated. MRI studies suggest that ALS could spread through vulnerable neuronal networks [73], and SOD1 and TDP-43 proteins possess prion-like domains, which might induce normal protein to change confirmation, leading to cell-to-cell transmission [74].

MANAGEMENT

There is no cure yet for ALS, so, while research continues, the objective of clinical care is to maintain quality of life and prolonging life as much as possible. Management is centered on a combination of a neuroprotective medication, multidisciplinary clinics and respiratory support. Controlled trials are needed to define the best timing and role for gastrostomy. Many therapies can help relieve symptoms, including anxiolytics and analgesics, which bring comfort in the advanced stages.

Riluzole

Riluzole was developed because it possesses anti-glutamatergic properties that might reduce exitotoxicity in ALS. Riluzole slowed disease progression in two randomized controlled trials [21,75], reducing mortality albeit modestly [76]. The most common side effects are diarrhea, dizziness, fatigue, nausea, and somnolence. Elevation of liver enzymes can occur, but rarely to levels that are clinically meaningful. Most patients in Europe, where the health systems pay the cost, and more than half of patients in the U.S. take riluzole [77].

Multidisciplinary care

Specialty clinics for ALS emerged in the 1980s and most large centers in developed countries currently offer multidisciplinary care [20]. Patients treated by ALS care teams may have higher quality of life [78] and longer survival [19].

Consensus guidelines help standardize diagnosis and treatment [79,80]. A neurologist oversees clinical evaluations, which are usually done every 3 months to ensure that problems are identified and treated expeditiously. Patients and families see professionals from different disciplines in one sitting, preserving energy and time. The level of experience is high because the teams see many patients with ALS, a rare disease. Patients receive information about advanced directives, treatments for nutritional and respiratory insufficiency, and research [20]. The education and support help patients decide ahead of time whether to choose life support and help guide the multidisciplinary team in setting goals for care. A standard team is highlighted in Table 2.

Additional staff available to clinics may include a respiratory therapist, a pulmonologist, a gastroenterologist, a psychiatrist, a neuropsychologist, and an orthotist. The neurologist formulates a treatment plan with the information gathered by the various professionals. The recommendations are conveyed to the patient's primary physician so that care continues in tandem.

Table 2. Standard evaluation in multidisciplinary consultation [31]

Multidisciplinary team members	Standard evaluation
ALS Nurse	Organizes and supervises the practice Welcomes and orients the patient Helps in various tests (weighing, measuring lung capacity). Oversees collection of clinical data
Dietician	Evaluates nutritional status and dietary needs. Advises means maintain caloric balance.
Occupational therapist	Evaluates dexterity and independence
Physical therapist	Evaluates motor function and safety; Assesses need for adaptive equipment.
Psychologist	Assesses the presence of anxiety-depressive disorders Provides a supportive environment Assesses cognitive disorders (memory, attention, concentration) Provides coping strategies
Social worker	Helps with disability plans, insurance, home care, advance directives Provides emotional support
Speech therapist	Evaluates the voice, speech and swallowing. Advises regarding alternative communication devices (communication boards, speech synthesis)

Nutrition and gastrostomy

Inadequate nutrition and dehydration, which become common as ALS advances [81,82], have multifactorial causes. Bulbar muscle weakness and dysphagia, arm weakness that limits the ability to lift the arm to carry food to the mouth, and hypermetabolism all contribute to negative calorie balance. Reduced lean body mass and less physical activity accentuate muscle turnover. The end result is weight loss, which can be rapid and lead to accelerated clinical deterioration [83]. The rate of weight loss may be a more important predictor of disease progression than being under or overweight at diagnosis [82].

Monitoring weight in the clinic is the simplest way to assess caloric balance. Calculation of body mass index

(BMI) using height and weight is also used. Recommendations vary according to symptom severity: Adaptations in food texture and postural changes such as the chin tuck are sufficient for mild dysphagia. Nutritional supplements can be tried once oral intake of adequate calories becomes difficult. When positive caloric balance is no longer possible by mouth, a gastrostomy is indicated.

While gastrostomy ensures ample nutrition, beneficial effects on quality of life and life expectancy have not yet been demonstrated [83,84] and there are no randomized controlled trials that examine the effect of gastrostomy in ALS. Some patients may agree to the procedure too late in the disease to receive meaningful benefit [85]. The ideal timing for gastrostomy awaits definition, but practice guidelines suggest that placement is safer while the vital capacity is above 50% of predicted [82,86]. Parenteral supplementation can be tried for those too ill to withstand a procedure [87].

Ventilatory support

When respiratory muscles become weak, symptoms of dyspnea, orthopnea, sleep fragmentation, daytime fatigue, and morning headaches develop. A forceless cough due to diaphragm and bulbar muscle weakness can lead to excessive secretions, poor airway clearance, and aspiration. Serial assessment of respiratory function includes history, physical examination, overnight pulse oximetry and vital capacity (VC). The maximal inspiratory and expiratory pressures (MIP and MEP) correlate with respiratory muscle weakness [86]. A MIP of <60 cm H2O is a predictor of reduced survival. Sniff nasal inspiratory pressure (SNIP), a noninvasive measure of inspiratory force, estimates intrathoracic pressure, is sensitive to respiratory muscle weakness, declines predictably over time, and predicts survival. A transcutaneous carbon dioxide sensor can detect elevated carbon dioxide levels due to muscle weakness [88].

The cause of death in ALS is normally respiratory. Approximately 60 % of patients have a predictable decline in function and the remainder die suddenly, sometimes from other causes [89].

Non-invasive ventilation (NIV) is an established treatment for patients with respiratory insufficiency [20]. The bi-level intermittent positive-pressure ventilator, which is triggered by a patient's inspiratory effort and shuts off during exhalation, facilitates physiological breathing. When used at least four hours per day, NIV reduces the work of breathing, improves gas exchange, enhances sleep quality [90], extends survival [91], and may improve cognition [92], as well as help stabilize weight. Oxygen is usually prescribed only in conjunction with NIV to prevent inhibiting respiratory drive in the setting of elevated serum carbon dioxide levels. Guidelines for prescription of NIV [86,93] are summarized in Table 3.

Table 3. Criteria for initiation of respiratory support in ALS patients

Presence of symptoms related to respiratory failure associated with one of the following objective criteria:	PaCO2 greater than 45 mm Hg and / or Vital capacity less than 50% of normal and / or Nasal inspiratory pressure and maximum pressure sniff below 60% of normal and / or Nocturnal desaturation below 90% PaO2 more than 5% of the time

Invasive ventilation may extend survival but requires 24-hour supervision, is expensive, and is ultimately chosen by fewer than 5% of patients [89,94]. Some long-term survivors progress to a total locked in syndrome in which all ability to communicate, even with eye movement, is lost. Some patients choose to have respiratory support withdrawn, a decision that is ethical as long as analgesics and anxiolytics are prescribed to avoid suffering when the ventilator is disconnected. Brain-computer interface technology is being tested in ALS (see below) because some patients retain the cognitive function needed to operate a computer using brain waves and biofeedback.

Diaphragm pacing is an approach to treating respiratory failure that is undergoing evaluation in ALS [95]. A system was approved by the U.S. Food and Drug Administration in 2011 for ALS, not because it was proven effective, but under a Humanitarian Device Exemption, which allows patients with a terminal illness to use an unproved but apparently safe device while awaiting the results of a clinical trial. Phrenic nerve pacing is available to patients with other disorders that cause hypoventilation but leave the phrenic nerve unaffected, such as spinal cord injury [96]. Phrenic nerve systems help maintain diaphragm strength by giving low-frequency stimulation via electrodes that are surgically attached to the nerve. Diaphragm pacing evolved from the nerve systems because the phrenic nerve degenerates in ALS [97]. A randomized controlled trial is currently recruiting patients in France.

An assisted cough device, suction machine, theophylline, antibiotics, mucolytics, and expectorants can help ease respiratory symptoms [98]. Pneumonia and influenza vaccines reduce pulmonary infections [86].

Table 4. Treatments used for ALS

Treatment	Administration	Indication
*Riluzole	50 mg bid	ALS
*Multidisciplinary care	Every three monthly visits	All symptoms of ALS
*Non-invasive ventilation	Nighttime and during symptoms at least 4 hours/day	Respiratory insufficiency
Gastrostomy	Daily calorie supplements	Dysphagia and malnutrition
*Dextromethorphan/quinidine	20mg/10mg bid	Pseudobulbar affect
Diaphragm Pacing	Up to 24 hours/day	Respiratory insufficiency
Brain-computer interface	Experimental	Communication
Amitriptyline	12.5-125 mg qhs	Anxiety
SSRI antidepressants	20-100 mg qd	
Mirtazapine	15-30 mg qhs	
Buspirone	10 mg tid	
Diazepam	2-10 mg tid	
Lorazepam	0.5-2 mg tid	
Mirtazapine	15-30 mg qhs	
SSRI antidepressants	10-100 mg qd	
Diazepam	2-10 mg tid	Cramps
Phenytoin	100-300 mg qhs	
Vitamin E	400 IU tid	
Mirtazapine	15-30 mg qhs	Depression
SSRI antidepressants	20-100 mg qd	
Tricyclic antidepressants	12.5-150 mg qhs	
Venlafaxine	37.5-75 mg qd	
Amantadine	100 mg qAM, qnoon	Fatigue
Bupropion SR	150-450 mg qd	
Fluoxetine	20-80 mg qd	
Pemoline	18.75-93.75 mg qd	
Pyridostigmine	60 mg tid	
Venlafaxine	75-225 mg qd	
Amitriptyline	12.5-125 mg qhs	Sialorrhea
Atropine sulphate	0.4 mg q4-6h 1-2 ophthalmic drops SL q4-6h	
Diphenhydramine	25-50 mg tid	
Hyoscyamine sulfate	0.125-0.25 mg q4h	
Scopolamine transdermal patch	0.5 mg q72h	
Baclofen	10-60 mg tid	Spasticity
Benzodiazepines	2-10 mg tid	
Dantrolene	25-100 mg tid	
Tizanidine	2-8 mg tid	
Amitriptyline	12.5-75 mg qhs	Urinary urgency
Oxybutynin	2.5-5 mg bid 3.9 mg patch qd	
Tolterodine	1-2 mg bid	

Bid = twice daily; IU = international units; qAM = every morning qd = daily; qhs = every day qt bedtime; qid = four times daily; qnoon = every day at noon; qxh = every x hours; SL = sublingual; SR = slow release; SSRI = serotonin-specific reuptake inhibitor; tid = there times daily.
*shown to have a beneficial effect in ALS

Symptomatic agents

Many medications, most used off-label, can reduce symptoms due to ALS (Table 4). Some treatments improve quality of life and a few appear to extend life.

Palliative care

All of ALS care is palliative because of the relentlessly progressive course. Open communication is the key to preparing patients for end-of-life decisions, and, even though discussions have become more matter-of-fact, the topic is still sensitive. Hospice can be especially helpful in providing a framework for conversations about life support.

The goal of ALS care in the terminal phases is to avoid suffering. Hospice teams provide symptom management through the use of medications, as well as emotional support for patients and families. Medications to relieve suffering such as anxiolytics and opioids, can be prescribed under the direction of a physician with knowledge of treating terminal diseases or a hospice team. Narcotic medications are effective for treating pain, dyspnea and nocturnal discomfort long before the final phase of the illness [99]. End-of-life palliation is usually done at home, but inpatient hospice wards can be used for patients who do not wish to die at home.

CLINICAL TRIALS

Since two randomized controlled trials showed the effectiveness of riluzole, more than 30 trials have ended in negative results [100]. This lamentable history over 18 years despite advances in other areas of ALS research has prompted researchers to create standard methodologies to improve animal studies [101] and human trials [16,102,103]. ALS is a complicated disease to study; the disorder is rare and heterogeneous, correct doses for neuroprotection are difficult to identify, outcomes are clinical and have high variance, and progressive weakness can lead to missing data [16]. An active search for biomarkers is underway so that diagnosis and measures of progression are more sensitive [104].

Current trails are targeting muscle proteins, seeking ways to stabilize energy expenditure, utilizing cell replacement therapies, and ascertaining whether abnormal genes can be silenced. Patients can find trials enrolling participants at www.clinicaltrials.gov.

Antagonsim of Nogo, a muscle protein that inhibits neurite outgrowth, might enhance reinervation in ALS [105]. Some studies suggest that exercise programs might have positive physiological and psychological effects for people with ALS, especially when implemented before muscular atrophy occurs [106]. One ongoing trial aims to determine the place for exercise in ALS.

Energy depletion also appears to influence the development of the disease, and is associated with worse prognosis [82]. Two clinical trials evaluating nutritional interventions are underway. The first trial is assessing a high fat diet given by tube feedings and the second is examining the safety and efficacy olanzapine, a drug that promotes weight gain.

Stem cell therapies are also being tested [107]. There is considerable scientific evidence that stem cells exercise a variety of beneficial effects in neurodegeneration, including in the ALS mouse model, and now phase I clinical trials are being conducted in patients to determine the safety and feasibility of transplantation using different types of stem cells. Cell therapy strategies utilize various types of stem cells to replace degenerating cells, support neurons and surrounding cells through release of neurotrophic factors, and study disease physiology. Possible sources of stem cells for ALS include bone marrow, neural stem cells, mesenchymal stem cells, astrocyte precursor cells, and induced pluripotent stem cells [108].

Stem cell models of neurodegeneration can be used to study the disease and to rapidly screen potential therapeutic compounds. Transplanted stem cells in animals and people appear to have an effect by supporting degenerating neurons and enhancing production of growth factors [109]. The cells might also be used as vectors for gene or drug therapy. Open questions include which stem cell type will be safest and most effective for use in ALS, as well as how to target both motor neurons and their surrounding astrocytes and microglial cells. Numerous exploratory trials are underway across the world, but the clinical administration of cell replacement is still in its infancy, and patients must guard against 'medical tourism' clinics that make unsubstantiated promises for expensive treatments [110,111].

Current trials are also aimed at genetic defects. The identification of mutations responsible for ALS has led to the advent of antisense therapy, which utilizes injections of short synthetically modified nucleic acid that binds to an mRNA target, silencing its function [112]. The molecules are too large to cross the blood-brain barrier and so must be administered by intrathecal injection. Antisense therapy reduces the expression of wild-type and mutated SOD1 protein in human cell cultures and transgenic animals [112]. In a recent phase I study, antisense therapy was given to 22 ALS patients harboring SOD1 mutations without toxic effects [113].

Testing New Agents and Trial Design

Riluzole extends survival by about 11% [76]. The only other clearly positive trial that tested efficacy of a medication was of the combination of dextromethorphan and quinidine (AVP-923; Nuedexta), which alleviated the symptoms of pseudobulbar affect in a multicenter, randomized, controlled trial [114]. Dextromethorphan modulates the presynaptic release of glutamate and dopamine by blocking the NMDA receptor and acting as an σ-1 receptor agonist. Quinidine was included because it inhibits the metabolism and, therefore, prolonging the half-life, of dextromethorphan. The combination is now commercially available.

A worldwide resource-intensive search is underway at the bench to improve understanding of ALS pathogenesis and physiology and in translational research to identify more effective neuroprotective therapies. New therapy development for ALS currently involves the twofold process of identifying potential neuroprotective agents in the laboratory and then testing them in human clinical trials. Summary articles on basic science techniques and clinical trial design are listed below.

Generating the scientific justification for a new agent entails evaluating the compound in *in vitro* models, which can include cell culture preparations and models of glutamate toxicity or mitochondrial dysfunction among others [104], followed by placebo-controlled trials in transgenic animal models to determine how an agent might affect the disease physiology. There is no model that perfectly recapitulates the human condition; many positive studies in animals could not be replicated in people, partly because of deficiencies in the design of the animal and human trials and partly because of the complex nature of ALS [16]. While other transgenic animal models are under development, the SOD1 rodent is still considered the gold standard for screening potential new drugs [115]. Standard approaches to testing agents in the model, including assessment of dose and pharmacokinetic profiles as well as the importance of publishing negative trials to avoid bias are now published [101]. Animal studies test mechanism, pharmacokinetics, and efficacy, ideally helping to refine the dose, route and regimen for human studies. A negative animal study suggests that more scientific work is needed to determine the best approach in the laboratory before dedicating the financial and human resources needed to test a new drug in humans. In sum, since no *in vitro* or *in vivo* system can guarantee success in humans ALS, consistency of preclinical data, identification of a credible mechanism, evidence of CNS penetration and efficacy in a well-designed animal trial are the foundation of suficient scientific rationale to study a new drug in people [116,117]. Adequate toxicology studies in animals also are needed before the US Food and Drug Administration will allow human trials.

Once adequate scientific justification for an agent is established at the bench, only robust clinical trials can ensure that the true effect of the agent is measured. The clinical trials process includes several phases. Phase-I studies, test pharmacokinetic characteristics and clinical safety as well as toxicity of the drug at a range of doses, usually in less than 100 human subjects.

Phase-II studies explore dose regimen, safety and toxicity, feasibility, and early evidence of efficacy or non-futility, and generally include up to several 100 patients. Dose-ranging is considered crucial in ALS [117-119]. Definition of the correct dose and regimen prior to embarking on an efficacy trial is difficult but without it, phase III trials can be fatally handicapped before they begin. The phase-II study seeking early evidence of efficacy, however, risks masquerading as an underpowered phase-III trial. Innovative pilot designs that act as efficient screens before proceeding to efficacy trials, can test multiple medications or doses at once and do so more efficiently than standard parallel group designs [120].

The phase-III trial is the final test of efficacy and safety and is usually undertaken in several hundred to several thousand patients. The ALS Functional Rating Scale (ALSFRS-R) and survival are clinical endpoints widely used to establish efficacy until biomarkers become available. Phase-IV studies are occasionally conducted once a drug has received marketing approval, with the goal of detecting rare, serious side effects that may have escaped detection in earlier phase studies.

The randomized double-blind placebo-controlled parallel study is the gold standard for testing efficacy, is simplest to interpret, and is needed for approval of a new medication in most countries. Typically, in this study design, patients are randomly assigned to one of two groups. One group of patients receives the drug to be tested, while the other group receives placebo (or the standard treatment). Both the patients and investigators are blinded to the assignments. The effects of different dose levels can be investigated in multiple parallel arms. The strengths of this design include the ability to randomize patients at the same stage of the disease for direct prospective comparison, and negation of the placebo effect because both blinded groups presumably experience the placebo effect to the same degree.

The randomized controlled trial is not fool-proof, however. Potential pitfalls include finding no difference in a study with low power and concluding that the two groups are equivalent, when in fact they are not. Such studies are not negative but inconclusive; not enough data were collected to detect a clinically important difference if one existed. Statistical planning prior to study roll out is necessary to decide on adequate power and effect size. Without known causes, neuroprotective drugs cannot

target the root triggers, and anticipated effects of any agent are small. Given the 11% impact riluzole, choosing an effect size of more than 15-20% in present trials may be unrealistic [118,121]. Trials powered to detect larger effects risk being too insensitive to detect small effects, positive or negative [121].

An important component of the trial is the day-to-day logistics of reducing missing data, minimizing subject dropout, accurate data collection and management, as well as clear analysis. Biomarkers of disease progression are not yet available for ALS, but including pharmacodynamic measures as part of a trial can improve understanding of the disease and provide insights into the effect of the drug [122].

Many past trials may not have been negative so much as inconclusive due missteps in the process, but each trial has improved our understanding of methodology and the scrutiny of their designs, strengths and weaknesses has helped direct present endeavors. Because ALS is a rare disorder, there are few patients who can participate in trials: a sound trial design is essential for the judicious use of resources. The riluzole trials used survival as the primary outcome measure, but survival trials need the greatest number of patients and study duration to discern a difference between groups. Survival is a robust outcome measure for Phase III trials, but survival trials are becoming increasingly difficult to perform as more agents are tested; surrogate outcomes are better suited for early phase trials especially. Other outcome measures can also reliably measure change over time.

The ALS Functional Rating Scale (ALSFRS-R) is an often-used endpoint because it predicts survival, is easily administered over the phone, thereby reducing dropout, is inexpensive and provides information on function, which may be more meaningful to patients than survival alone [123].

Since the early 2000s, trials have also explored different statistical methods to enhance efficiency in drug testing in ALS. A Phase III trial of creatine using survival as the primary outcome measure called attention to sequential data monitoring by an independent unblinded statistician who was able to stop the trial 18 months earlier than expected when a positive outcome was no longer statistically possible [124]. This method saved human and financial resources compared to a standard fixed duration design. Other designs are being tried in early phase trials [125,126]. A Phase II selection trial is conducted between two or more experimental arms, with the aim of choosing the empirically superior treatment at the end of study. This design differs from a conventional trial, which requires proof of a statistically significant difference between arms. The selection design allows investigators to screen multiple agents or doses in small sample size trials to identify the most likely to succeed before proceeding to large efficacy trials. Another approach is the non-superiority or futility design in which the hypothesis statement is reversed and superiority is assumed. If the decline in an outcome such as ALSFRS-R is less than a predetermined percentage, then the null hypothesis of superiority is not rejected, inadequate evidence of futility is concluded, and the drug is deemed eligible for a Phase III trial. The futility design permits investigators to protect against falsely rejecting a drug as ineffective due to inadequate power, while at the same time providing reassurance of a reasonable likelihood of success in a well-powered efficacy trial. These phase II designs have not, so far, led to false positive results the way standard parallel group phase II trials have, and guard against the fatal flaw in phase II design of mimicking a phase III trial but with lower power.

FUTURE DIRECTIONS

Disease propagation

The future lies in finding causes for sALS and, until then, elucidating how the disease spreads in the brain once initiated; stopping either process could halt the disease. Similar to other neurodegenerative disorders, affected neurons in ALS contain aggregated protein inclusions. The focal onset and contiguous spread of the disease clinically is mirrored by migration of misfolded protein in degenerating neurons in the brain [18]. In ALS, the inclusions occur first in motor neurons in the cortex and brainstem. In patients with ALS and dementia, the inclusions are found throughout the frontal and temporal lobes. Some of these proteins may have prion-like domains. They are not infectious like true prions, but have a propensity to self-aggregate, and act as templates for normal protein, inducing conformational changes in previously unaffected protein. The change in conformation in normal protein appears to result in migration from diseased to healthy cells. Protein aggregates are themselves associated with other pathophysiological processes such as mitochondrial dysfunction and energy depletion, glutamate excitoxicity, and induction of inflammatory mediators. Misfolded protein could be a target for therapeutic intervention [74] and a breakthrough in one neurodegenerative disorder would likely translate rapidly to other disorders.

Brain Computer Interface

As ALS advances, patients can lose the ability to communicate. Bulbar symptoms can progress to anarthria making meaningful voice communication impossible; motor function can deteriorate so that the ability to operate a computer with the limbs is lost; and eventually

communication using eye movement is no longer possible. Ultimately, some patients become completely locked in, unable to move any voluntary muscle.

Considerable research is being done to enable patients with ALS to continue to communicate and even operate aids to assist in daily functions using brain-computer interfaces (BCI)[127]. BCIs measure brain activity and translate it into directions that control a computer. Most clinical applications use biofeedback to teach patients to control brain wave output; computers interpret brain wave activity and patients can learn to regulate the activity to achieve goals through the computer. The technology can be used to provide patients with a device that does not rely on muscle activity. Learning BCI appears to involve the same brain systems and information processing as other skills. Patients can learn to spell using a virtual keyboard and to move virtual limbs.

Despite widespread degeneration in ALS, skill learning seems to remain intact up to the very final stages [128]. A downside to the technology is that the systems with high accuracy and speed also place great demand on attention and memory. In some patients, cognitive deterioration may make operating a BCI impossible.

Several clinical studies examining various BCI technologies in ALS are currently enrolling patients. A feasibility study of an intracortical neural interface being done in the U.S. aims to determine the safety of the system and to describe the algorithms and outcomes needed for a larger trial. The device is implanted onto the motor cortex of patients and neuronal recordings are made over time. An EEG-based BCI using scalp recordings that assist patients with severely advanced ALS is being studied in Philadelphia. This trial is expected to conclude in 2014. A study in France is testing severely progressed patients' ability to communicate via spelling using summed brain potentials and is expected to finish in 2015.

SUMMARY

In 2013, ALS is still so rapidly progressing that it is physically and emotionally overwhelming for patients, families and care givers. Health care teams spend their time helping patients cope and trying to keep pace with a disease that produces new degrees of impairment and disability almost without pause. Current care is multidisciplinary and includes respiratory support, supplemental feeding, and riluzole, which appear to extend survival modestly. Symptomatic medications can improve quality of life, but more need to be tested in trials for ALS. Numerous potential neuroprotective agents targeting pathophysiological processes have been studied, but there have been no recent successes.

Yet, hope seems almost around the corner. Scientific advances have uncovered several important genetic causes and much about the disease physiology. Important ways to intervene in the pathophysiology, including supporting or replacing degenerating cells, slowing the spread of aggregated protein, and silencing mutated genes could have clinical impact soon. Clinical trials are becoming increasingly sophisticated so that the effect of new therapies is determined accurately.

As new theories shed increasing light on the physiology, we await the next great breakthrough; discovery of the causes of sALS and the medicines that follow. Meanwhile, patients are offered modern care that can help ensure comfort and dignity during this most difficult disease.

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