

A Systematic Review of the Effect of Moderate Intensity Exercise on Function and Disease Progression in Amyotrophic Lateral Sclerosis

Andrew J. Lui, PT, DPT, and Nancy N. Byl, PT, MPH, PhD, FAPTA

Background and Purpose: Amyotrophic lateral sclerosis (ALS) is an idiopathic disease of adults affecting upper and lower motor neurons. In one to four years, progressive weakness, spasticity, and respiratory insufficiency compromise independence and survival. Current medical treatment is limited to medication and supportive care. The benefit and harm of moderate physical exercise are controversial. This review examined current research related to moderate exercise for maintaining independence without accelerating disease progression in persons with ALS.

Methods: An evidence-based search was conducted using keywords alone and in combination (ALS, exercise, Lou Gehrig's disease, physical therapy) to search PubMed, PEDro, Hooked on Evidence, Ovid, and Cochrane databases. Human and animal models were included and graded on level of evidence and strength of recommendations for developing guidelines to practice. A secondary reviewer evaluated all selected studies, and statistics were calculated.

Results: The search yielded the following nine studies: four small clinical studies, one clinical systematic review, and four randomized, controlled trials based on animal models. In human studies, there were small to moderate effect sizes supporting the benefit of moderate exercise in persons with early-stage ALS, with no adverse effects on disease progression or survival time. In transgenic mice with superoxide dismutase-1 ALS, moderate exercise most often had a moderate effect size for increasing life span.

Discussion and Conclusion: Large randomized clinical trials are needed to develop specific exercise guidelines. However, evidence suggests that moderate exercise is not associated with adverse outcomes in persons with early-stage ALS. Moderate exercise programs can be safely adapted to abilities, interests, specific response to exercise, accessibility, and family support.

Key words: amyotrophic lateral sclerosis, exercise, Lou Gehrig's disease, physical therapy

(*JNPT* 2009;33: 68–87)

Department of Physical Therapy and Rehabilitation Science, UCSF/SFSU Graduate Program in Physical Therapy, San Francisco, California.

Address correspondence to: Andrew J. Lui, BS, MPT, DPT, PT, E-mail: lui@ucsfmedctr.org

Copyright © 2009 Neurology Section, APTA

ISSN: 1557-0576/09/3302-0068

DOI: 10.1097/NPT.0b013e31819912d0

INTRODUCTION

The Problem

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and ultimately fatal neurodegenerative disorder of unknown etiology that involves the loss of upper motor neurons (UMNs) and lower motor neurons (LMNs) in the cerebral cortex, brainstem, and spinal cord.^{1,2} It is the most common motor neuron disease in the adult population with a prevalence of two to seven cases per 100,000 individuals.³ The worldwide incidence rate is reported to be 0.6 to 2.6 per 100,000.^{4,5} It affects males 1.5 to two times as often as females.⁶ Both incidence and prevalence rates of ALS increase with age until the seventh and eighth decades; the lifetime likelihood of mortality from ALS is 1:1000.⁵ In the past two decades, treatment has not significantly increased survival rates for persons with ALS. The median survival after diagnosis of ALS varies from one to four years.^{1,7} Death occurs, on average, three to five years after the first symptoms of respiratory failure.⁸

ALS is characterized by progressive weakness, atrophy, fatigue, spasticity, dysarthria, dysphagia, and respiratory compromise, which lead to progressive functional limitations, disability, and ultimately mechanical ventilation or death.⁴ Despite recent advances in understanding the pathophysiology of ALS, the cause and pathogenesis of ALS remain elusive.⁹ Most commonly, ALS is idiopathic, but 10% of the time, it is familial with an autosomal dominant inheritance.¹⁰ There is currently no medical treatment that reverses or halts the progression of the disease.¹ The mainstay of treatment for persons with ALS remains pharmacologic and symptomatic management by a multidisciplinary medical team.^{9,11}

Relevance to Physical Therapy

In addition to seeking medical management strategies for functional limitations, many persons with ALS inquire about exercise as a means to delay loss of strength, endurance, and functional independence.¹ As members of multidisciplinary teams, physical therapists address progressive loss of function and independence in persons with ALS and other neurodegenerative diseases.¹¹ Moderate exercise programs are generally recommended for persons with neurodegenerative diseases.¹² These programs can include strengthening to address weakness, flexibility routines to minimize contractures, walking programs (with or without assistive

devices), and/or cardiovascular routines to maintain endurance.¹² However, the effects of exercise in persons with ALS are not well understood. Physical therapists must know the risks and benefits of moderate exercise to prescribe an appropriate intervention program that is safe and beneficial for persons with ALS.

The purpose of this evidence-based review was to evaluate the research in basic (animal) and clinical (human) science to determine the benefit and harm of moderate exercise intervention, including strength training and conditioning exercise, in persons with ALS. Given the low prevalence of ALS, the idiopathic nature of the disease, and the high morbidity and mortality associated with ALS, this evidence-based review included clinical systematic reviews, meta-analyses, randomized clinical trials, experimental research studies, and animal research models.

BACKGROUND: REVIEW OF THE LITERATURE

Clinical Features of ALS

Pathology in ALS is characterized by progressive death of UMNs in the motor cortex and corticospinal tracts, and the LMNs in the anterior horn cells in the spinal cord and brainstem nuclei for cranial nerves V, VII, IX, X, and XII.⁴ See Table 1 for a summary of clinical signs and symptoms of ALS. The most common symptoms associated with UMN loss are hypertonicity, difficulty with initiating and controlling movements of the effected area, slow speech, brisk gag and jaw jerk, brisk reflexes, and Hoffman's or Babinski's sign.⁸ The primary symptoms of LMN loss are muscle weakness, atrophy, fasciculations (twitching), cramping, and secondary fatigue. Any combination of these symptoms may occur in the bulbar, cervical, thoracic, and/or lumbosacral regions at various phases of the disease.^{6,11}

Symptoms of ALS most commonly start as asymmetric focal distal weakness in one limb that spreads first to adjacent groups of motor neurons, which then moves axially.¹ About 40% to 50% experience initial signs and symptoms in the upper extremities. The onset of signs and symptoms occurs in the lower extremities in approximately 40% of individuals. In the remaining 10%, onset may be characterized by signs and symptoms of the bulbar region (ie, excess saliva, excessive laughing, slurring of speech, difficulty swallowing, and/or difficulty breathing).¹¹ Up to 50% of persons with ALS will at some point demonstrate signs of pseudobulbar affect, including exaggerated or uncontrolled laughing or crying.⁸ Initially, persons with ALS may be diagnosed with other musculoskeletal problems surrounding previous sports-re-

lated injuries or degenerative musculoskeletal conditions that lead to a surgical intervention (eg, spinal fusions or joint replacements). Ultimately, the combination of progressive neuromuscular signs and symptoms leads to the diagnosis of ALS.⁶

In ALS, there is usually sparing of the sensory system and preservation of oculomotor, bowel, and bladder functions.⁶ Although early studies indicated preservation of cognitive function in persons with ALS, more recent studies have suggested that up to 25% of these individuals have some signs of frontotemporal dementia.¹³

Specific Diagnosis of ALS

There are no unequivocal diagnostic tests for any form of ALS.⁴ Thus, the diagnosis of ALS is considered a clinical diagnosis.¹¹ The insidious nature of ALS makes diagnosis at symptom onset difficult. A period of observation is essential to make an accurate diagnosis.⁸ The World Federation of Neurology (WFN) developed criteria to ensure diagnostic accuracy.¹¹ The person must have the following four clinical features: signs and symptoms of UMN loss, signs and symptoms of LMN loss, steady progression of symptoms within one body region and ultimately other body regions, and exclusion of symptoms inconsistent with ALS (Table 2 for WFN criteria).^{4,6,11}

The WFN criteria also specify levels of certainty of diagnosis based on progression of UMN and LMN signs. These criteria also acknowledge the role of electrodiagnostic (ie, electromyography) and imaging studies (ie, magnetic resonance imaging) to increase diagnostic certainty early in the course of the disease. Specifically, electromyographic findings in ALS characteristically show diffuse denervation that cannot be explained by a focal lesion.¹¹ Magnetic resonance imaging is typically used to exclude focal lesions as the cause of UMN findings in ALS, but may also be used to measure atrophy of the gray matter in the premotor cortex and the basal ganglia.¹⁴ Laboratory studies are used to exclude other diseases that may have a clinical presentation similar to ALS (ie, neoplasms, Lyme disease, endocrine disorders, myopathies, radiculopathies).⁸ Using these guidelines, diagnostic accuracy (specificity for diagnosing ALS) has been estimated to be 95%.¹¹

Pathogenesis of ALS

Several possible genetic, environmental, and other factors have been identified to help clarify the diagnosis of ALS.¹⁵ Approximately 5% to 10% of persons with ALS have family members affected by the disease (familial

TABLE 1. Impairments and Functional Clinical Signs and Symptoms of ALS⁴

Impairments	UMN Signs	LMN Signs	UMN and LMN Signs	Unusual Manifestations
Degenerating motor neurons	Weakness	Weakness	Dysarthria	Dementia
Atrophy of muscle cells	Spasticity	Muscle wasting	Dysphagia	Sensory dysfunction
	Hyperreflexia	Muscle cramps	Fatigue	Oculomotor dysfunction
	Pathologic reflexes	Fasciculations	Respiratory insufficiency	Autonomic involvement
	Pseudobulbar affect			Pain

TABLE 2. World Federation of Neurology Criteria for Diagnosis of ALS¹¹

Presence of All of the Following:	Together with Absence of the Following:
Signs of LMN degeneration by clinical, electrophysiologic, or neuropathologic examination	Electrophysiologic evidence of other disease processes that might explain the signs of LMN or UMN degeneration
Signs of UMN degeneration by clinical examination	Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiologic signs
Progressive spread of signs within a region or to other regions (bulbar, cervical, thoracic, lumbosacral)	

The diagnosis of ALS is made clinically in the absence of objective electrophysiologic or imaging evidence of other diseases.
Abbreviations: LMN, lower motor neuron; UMN, upper motor neuron.

ALS). This is almost always transmitted as an autosomal dominant trait.⁶ In 20% of persons with familial ALS, the disease is caused by a mutation in the superoxide dismutase (SOD)-1 gene.⁸ This genetic mutation decreases the ability to protect nerve cells from damage caused by the free radicals resulting from the byproducts of oxygen metabolism. A genetic susceptibility has also been suggested by epidemiologic data showing an association among ALS, dementia, and Parkinsonism in certain families.¹⁵ A markedly higher incidence and prevalence rate of ALS exists in certain populations in different parts of the world. This suggests environmental causes such as exposure to toxins (ie, heavy metals, chemicals), electric shock, or electromagnetic fields, ingestion of certain foods or toxins, persistent viral or prior infection, or excessive physical exertion.⁵ In addition, other researchers suggest autoimmune dysfunction, excessive levels of glutamate, or neoplastic syndromes as possible causes of ALS.¹⁶ Some investigators also report an association between cumulative physical activity and the risk of ALS (eg, 10 years before diagnosis). Although there is some association between a high level of physical activities during work or leisure time activities and onset of ALS in susceptible individuals, there are no large, multicenter epidemiologic studies to confirm this relationship.¹⁷

As yet, the etiology and risk factors for a nongenetic pathogenesis of ALS remain uncertain.¹⁵ In light of the diverse findings, there is growing acceptance that ALS may be multifactorial in etiology and pathogenesis.¹⁵ The primary mechanisms of cell death in motor neurons in persons with ALS range from disruption in free radical homeostasis through SOD-1 mutations to disorganization of intermediate cellular filaments, abnormalities of intracellular calcium regulation, including glutamate-mediated excitotoxicity, and imbalance of regenerating and degenerating motor neurons.¹⁵ Thus, an animal model using transgenic mice with mutations at the SOD-1 gene is most commonly used to explore the pathophysiology of ALS.^{4,18}

Pathogenesis of Fatigue Relevant to Exercise in Persons with ALS

It is difficult to separate the parameters of weakness and fatigue in persons with ALS. For example, neuronal degeneration creates muscle weakness, fatigue, and hypertonicity. Some fatigue seems to be directly related to changes in the skeletal muscle itself.¹⁹ Peripheral denervation, for example, leads to structural damage of the muscle fiber, decreasing

mechanical force output and secondarily creating weakness and fatigue. In human models, myoelectrical fatigue, a reduction in muscle fiber conduction velocity (force fatigue index) has also been reported.²⁰ This myoelectrical fatigue primarily affects type II fast motor unit muscle fibers more than types I and III.^{19,20} In animal studies, the neurons controlling fast fibers were noted to degenerate early in the course of ALS, whereas fatigue resistant neurons failed in the intermediate stages of ALS and slow twitch neurons (the S fibers constantly used in the trunk) failed in the later stages.^{21–23} Although these specific findings have not been reported in human studies, these findings may serve as a guide when designing an appropriate exercise program.

Mitochondrial abnormalities in the DNA further contribute to muscle weakness and fatigue in persons with ALS.^{8,24–26} These DNA changes interfere with mitochondrial function of muscle during exercise.²⁴ Increased maximal oxidative phosphorylation capacity of mitochondria and decreased mitochondrial respiratory activity in muscle are associated with advancing severity of ALS.^{25,26}

Hypertonicity can also contribute to fatigue in persons with ALS. Typically, spasticity interferes with voluntary motor control, requiring the individual to exert more energy to complete a motor task. Involuntary and excessive contractions of postural muscles can be associated with pain and local and general fatigue even when normal muscle strength is present, but are especially important in persons with progressive weakness.^{27,28}

Ideally, exercise programs would address the underlying pathophysiology of ALS, including slowing the degeneration of motor neurons, minimizing stress on fast twitch muscle fibers, decreasing hypertonicity, strengthening weakened muscles, minimizing fatigue, facilitating musculoskeletal endurance, and enhancing cardiopulmonary efficiency. However, the effects of different exercise programs on the pathophysiological mechanisms implicated in ALS are not completely understood.²⁹ Examining the pathophysiology of exercise in ALS would require a longitudinal randomized clinical trial comparing exercising participants with nonexercising controls; clinical disease progression (as measured by strength, function, respiratory capacity, endurance, and severity of spasticity) would need to be monitored, along with concomitant physiologic changes in the motor units. A similar study using an animal model would need to be carried out to measure the effect of different types of exercise programs specifically on fast twitch muscle fibers.

Disease Progression and Prognosis

Ultimately, most persons with ALS reach a state wherein they are unable to walk, care for themselves, speak, or swallow.⁴ Although the progression of ALS tends to be relentless and steady, ALS is known to be heterogeneous with respect to progression; patterns and rates of disease progression vary markedly by geographic location, gender, culture, and other individual differences.³¹ As such, survival rates in persons with ALS show considerable variation. Five-year survival rates vary from 7% to 40%, whereas 10-year survival rates range from 8% to 16%. The median survival rate of persons with ALS from the time of symptom onset to death is 23 to 48 months; median survival time shortens to 12 to 23 months if measured from the time of diagnosis.^{1,7} Population-based studies have identified several prognostic factors associated with shorter survival after the diagnosis of ALS. These include the following: older age at onset, female gender, bulbar features at onset, and shorter time from symptom onset to time of diagnosis (suggesting more rapid progression).^{6,7}

Several methods of measuring disease progression in persons with ALS have been identified: muscle strength assessment by manual muscle testing (MMT), hand-held dynamometry, and maximum voluntary isometric contraction using strain gauges; respiratory muscle function assessment by spirometric measurement of forced vital capacity (FVC) or maximum inspiratory force; functional independence assessment by disease-specific rating scales, such as the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALS-FRS) or by general functional measures, such as the Functional Independence Measure (FIM); and disease-specific scales assessing both function and symptoms concurrently, such as the Norris ALS Scale.^{1,32} A variety of intermediate outcomes in addition to survival rates may be used to monitor the effectiveness of different strategies of intervention for ALS.

Treatment of ALS

Medical Treatment

Medical treatment for ALS focuses on slowing disease progression, symptom management, multidisciplinary treatment, and managing end-of-life issues. Currently, there are no medical management strategies that stop or reverse the progressive loss of motor neurons in ALS.^{1,8} Riluzole, a glutamate antagonist, is the only drug available in the United States that has been approved by the U.S. Food and Drug Administration to be safe and effective for treating ALS. It has been shown to slow the decline in muscle strength and lengthen median survival by 83 days.¹ Antioxidants, such as vitamins C and E, β -carotene, and α -lipoic acid are also prescribed, but their effect on disease progression has not been proven in clinical studies.⁸ A randomized clinical trial on coenzyme Q₁₀, a mitochondrial cofactor and antioxidant, was recently completed; unfortunately, this drug was reported not to be sufficiently promising to warrant further study for the treatment of ALS.³³ Trials are also underway studying the effectiveness of lithium,³⁴ ceftriaxone, glycosides,³⁵ memantine,³⁶ and talampanel.³⁷ Animal models using transgenic mice that overexpress the SOD-1 mutation have been instrumental in the search for ALS treatments.¹⁸ However, effective

tive treatment for the primary disease process in ALS is limited, and survival rates and life span of persons with ALS have not improved in the past two decades.^{7,8,11,38}

Current medical management primarily involves supportive care to manage symptoms of weakness, fatigue, bulbar dysfunction, spasticity, pain, depression, and respiratory failure.⁴ Multidisciplinary ALS clinics have been developed to help individuals maximize their comfort and independence in light of progressive disability. For these multidisciplinary teams, the primary goals in caring for persons with ALS are to treat the symptoms of ALS, improve the quality of life, and help caregivers and the family cope with the disease.¹¹ These multidisciplinary clinics have been associated with increased median survival rates for the persons with ALS (ie, 7.5 months increased survival for persons with general ALS versus 9.5 months for persons with bulbar ALS).¹ Simmons et al³⁹ also encourage physicians to listen to requests to participate in complementary and alternative intervention strategies even though there is little evidence to support their benefit in terms of disease progression.

A recent Cochrane Database systematic review searched for evidence of the effectiveness of treating spasticity in persons with ALS.⁴⁰ This review included all randomized and quasi-randomized trials regarding nonmedical, medical (prescription and nonprescription medications, chemical neurolysis), surgical treatment (intrathecal pumps), physical therapy, modalities, and alternative therapies (reflexology, aromatherapy, relaxation techniques) for reducing spasticity.⁴⁰ After screening based on rigorous criteria for randomized, blinded clinical trials with reliable outcome measures, only one exercise study met all of the criteria for inclusion. Based on a three-month change in severity of spasticity as measured by the Ashworth Scale, spasticity increased in the control group (effect size, 0.25; 95% CI, -0.46 to 0.96) and decreased in the treated group (effect size, -0.43; 95% CI, -1.03 to 0.17). The absolute risk reduction was -0.68 ($P < 0.05$). Only two participants would need to be treated with the exercise program to have one more person benefit from a reduction in spasticity. However, at six months, there were no significant differences between the remaining participants in each of the groups.

Physical Therapy Treatment and Exercise Prescription

Physical and occupational therapy are commonly involved in the care of persons with ALS.⁴¹ In light of the progressive nature of ALS, the goals of physical therapy treatment focus on optimizing independence and comfort for these individuals. Sinaki and Mulder^{42,43} developed rehabilitation guidelines for persons with ALS based on a six-stage model of progressive functional limitation (Table 3).

Therapy for persons with ALS traditionally includes the provision of education to the individual and caregiver education in safety and fall prevention, energy conservation, positioning-pressure relief techniques, and range of motion programs to prevent musculoskeletal pain.⁴³ In addition, environmental modification, functional mobility training, walking programs, cardiopulmonary physical therapy techniques, range of motion exercises, strengthening exercises,

and recommendations for appropriate adaptive equipment and community resources are the mainstay of physical therapy for this population.^{44,45}

Historically, general strengthening and conditioning exercises have not been recommended as the standard of care for persons with ALS. Early studies recommended that persons with ALS avoid exercise other than the exercise inherent in everyday ambulatory activities.⁴³ These recommendations were based primarily on epidemiologic studies indicating that high levels of physical exertion may be associated with an increased risk of progressing the degeneration associated with ALS.¹⁷ Some studies also described abnormal physiologic responses to exercise in persons with ALS.^{29,46,47} In particular, vigorous exercise could facilitate some of the pathogenic mechanisms implicated in ALS (eg, glutamate-mediated excitotoxicity, excessive inflammation and swelling, disturbances in free radical homeostasis).⁴⁸ High-intensity or highly repetitive physical activity could also increase muscle degeneration, permanent loss of strength, and motor neuron denervation.^{49–52}

On the other hand, some researchers suggest that moderate exercise programs could be beneficial rather than harmful for persons with ALS. Recent epidemiologic studies report no significant association between physical activity and the risk of progressing ALS.¹⁷ In fact, a case report noted improved isometric strength in most muscle groups in a person with ALS who participated in a proprioceptive neuromuscular facilitation exercise program.⁵³ Although there are compromises in muscle performance relative to the loss of innervation of muscles and associated muscle fiber physiology related to ALS, moderate exercise may have a beneficial effect on free radical balance and oxidation of muscle fibers to help modulate an excitotoxic environment.⁴⁸ Studies of persons with other neuromuscular diseases using low- to moderate-intensity strength and aerobic exercise programs have shown beneficial effects.^{49–52} However, because of marked differences in pathology, the effects of exercise in other neuromuscular diseases may differ significantly from

those in ALS. Still, when taken together, these studies suggest that exercise may be an appropriate treatment for persons with ALS.

The purpose of this review was to locate current evidence supporting the benefit versus harm of moderate exercise for persons with ALS. The primary question was as follows: In persons with ALS, does moderate exercise (ie, strengthening or conditioning/cardiovascular exercise programs) compromise functional status or accelerate disease progression?

This is a foreground question. The following criteria needed to be addressed in the studies selected to answer the primary question (PICO).^{55,56}

Population: Persons with possible, probable, or definite ALS; transgenic animal models.

Intervention: Exercises, including strength training (eg, isometric, isotonic, or isokinetic) and conditioning training (eg, sustained exercise including stationary bicycle, treadmill walking at or below anaerobic threshold).

Comparison group: Persons/animals with ALS only performing usual daily activities.

Outcomes: Disease progression, as measured by functional scores, and muscle strength and respiratory function in humans; as measured by motor function scores and life span in animals.

The null hypotheses tested in this review included the following.

Ho 1: Moderate-intensity strength or conditioning exercise programs do not significantly change functional status in persons with ALS.

Ho 2: Moderate-intensity strength or conditioning exercise programs do not have adverse effects on disease progression in persons with ALS.

Because ALS is a relatively rare and terminal disease, it was anticipated that there would be very few controlled, randomized clinical trials with a sufficiently large sample size to answer the primary questions. Because the disease is relentlessly progressive and quickly decreases function and

TABLE 3. Rehabilitation of Individuals with ALS at Different Stages of the Disease⁴³

Stage	Clinical Features	Activities	Equipment
I	Ambulatory, no problem with ADL, mild weakness	Normal activities; moderate exercise in unaffected muscles; AROM	None
II	Ambulatory, moderate weakness in certain muscles	Modification in living; modest exercise; A and AAROM	Assistive devices
III	Ambulatory, severe weakness in certain muscles, mild/moderate limitation of function	Active life; A, AA, and PROM; joint pain management	Assistive devices, adaptive devices, home equipment, wheelchair
IV	Wheelchair confined, almost independent, severe weakness in legs	PROM, modest exercise in uninvolved muscles	Assistive devices, adaptive devices, home equipment
V	Wheelchair confined; dependent; pronounced weakness in legs, severe weakness in arms	PROM, pain management and decubitus prevention	Adaptive devices, home equipment, wheelchair
VI	Bedridden, no ADL, maximal assistance required	PROM, pain management, decubitus prevention, DVT prevention, pulmonary hygiene	Adaptive devices, home equipment

The ALS disease process can be divided into six stages based on functional impairment in axial and appendicular muscle. Rehabilitation is matched to the stage of the disease process and individual/family goals.

Abbreviations: ADL, activities of daily living; AROM, active range of motion; AAROM, active assisted range of motion; PROM, passive range of motion; DVT, deep vein thrombosis.

ability to exercise,⁴⁵ it was also expected that many studies would have incomplete follow-up with limited ability to support or negate the benefits of exercise for persons with ALS. However, randomized, controlled animal studies using SOD-1 transgenic mice were expected to have sufficient follow up postintervention to draw conclusions. As such, this review included both human and animal studies.

Although ALS is a progressive neurodegenerative disorder compromising the motor neuron pool and secondary muscle fiber physiology,⁴⁶ the underlying theoretical construct is that moderate exercise may be safe and possibly beneficial for persons with ALS. Exercise adapted according to each individual's exercise capacity should avoid overload of the nervous, muscular, and respiratory systems, and activation of the pathophysiologic mechanisms of ALS (ie, alteration of free radical homeostasis, mitochondria function, organization of intermediate cellular filaments, or intracellular calcium regulation). Moderate exercise can improve neuronal plasticity through mediating trophic factors such as brain-derived neurotrophic factor,⁵⁷ insulinlike growth factor (IGF)-1,⁵⁸ and glial-derived entrophic factor.⁵⁹ Cardiovascular conditioning enhances cerebrovascular and peripheral circulation by increasing aerobic capacity through increased stroke volume and oxygen extraction, new capillary networks,⁶⁰ and increased choline uptake and dopamine receptor density.⁶¹ Thus, it is also possible that moderate exercise in ALS could be beneficial to healthy α -motor neurons by creating dendritic restructuring, increasing neurotransmitter release from the motor end plate, enhancing protein synthesis, strengthening synaptic connections to target muscles, helping maintain organization and firing potential of muscle fibrils, mediating intracellular calcium balance, and improving axonal transport.⁶²

Even if moderate-intensity exercise did not increase survival, it could potentially slow loss of strength, endurance, fatigue, and contractures. This deceleration of physiologic changes could secondarily maximize functional independence. Exercise also has known endorphin and metabolic benefits that may allow individuals to continue to engage in social interactions and enhance self-esteem and self-worth despite progression of physical impairments.

SEARCH METHODS

Sources for Evidence-Based Search

The evidence-based search for relevant studies was conducted by one researcher using PubMed, Cochrane Library, PEDro, Hooked on Evidence, and CINAHL. All the studies cited were found on PubMed (www.ncbi.nlm.nih.gov/pubmed) or CINAHL (gateway.ut.ovid.com). PubMed is an online service of the National Library of Medicine and provides public access to MEDLINE. CINAHL is an online service of the Ovid database.

Keywords

The search terms *amyotrophic lateral sclerosis* and *exercise* yielded 46 studies in PubMed and 18 studies in CINAHL. Combinations of the following search terms were also used: motor neuron disease, Charcot's disease, Lou

Gehrig's disease, ALS, exercise movement techniques, exercise therapy, physical therapy, and physical therapy techniques. PubMed includes citations that date back as far as 1966, and CINAHL includes citations as early as 1982.

Criteria for Studies to Be Included in the Search

Studies were collected from September 2005 to May 2008. Only studies available in English were included in the review. Studies using the El Escorial criteria for possible, probable, probable with laboratory support, and definite ALS were included.¹¹ The remaining criteria applied to select a study are outlined in Tables 4 and 5.

Because of a paucity of randomized clinical trials in human studies and the availability of acceptable animal models developed for studying ALS, mouse studies testing exercise protocols were also included in the review. Transgenic animal models based on the SOD-1 gene mutation have allowed researchers to study the pathogenesis of ALS and the physiological effects of different interventions including pharmaceutical agents, gene therapy, stem cell transplantation, and exercise in terms of disability, survival rate, and life span.¹⁸

The primary author collected all the published studies to be included in the review. A second independent reviewer applied the same criteria to determine whether the studies met the inclusion criteria. Five human studies and four animal studies met all the criteria and were included in this review.

Grading the Level of Evidence of the Studies

The primary author determined the level of evidence for each study according to Sackett et al,⁵⁵ as outlined in Table 6. This was used for the synthesis of best evidence. To assess the grading of evidence and interpretation of results, the findings were evaluated by a second independent reviewer and two faculty members at the University of California, San

TABLE 4. Criteria for Accepting Human Studies in Evidence-Based Review

Study Parameter	Criteria
Diagnosis	ALS (possible, probable, definite)
Types of intervention	Strength or aerobic vs no additional exercise
Level of evidence ⁵⁵	1a–3b (meta-analyses, RCT, cohort studies, good case study)
Experimental groups	Experimental vs control (2 group) or single group design
Number of subjects	No criteria
Assignment/blinding	No criteria
Outcome measures	Functional scores, muscle strength, respiratory function, disease progression
Length of study	At least six month follow-up
Ability to calculate evidence-based statistics	No criteria

Meta-analyses; randomized, controlled trials; and cohort studies were preferred. Studies of any size even without random assignment or blinding were eligible. Abbreviations: RCT, randomized controlled trial.

TABLE 5. Criteria for Accepting Animal Studies in Evidence-Based Review

Study Parameter	Criteria
Diagnosis	SOD-1 transgenic mice (ALS)
Types of intervention	Strength or aerobic vs no additional exercise
Level of evidence ⁵⁵	Five per Sackett et al ⁵⁵ (must be a meta-analysis or a RCT)
Experimental groups	Experimental vs control
Number of subjects	No criteria
Assignment/blinding	Random assignment
Outcome measures	Onset of motor symptoms, motor function measures, life span
Length of study	Life span of mice
Ability to calculate evidence-based statistics	Able to calculate % differences or survival curves for survival time or motor function

Meta-analyses and randomized, controlled trials were preferred. For animal research studies to be accepted there had to be a control group and sufficient survival or motor function data.

Abbreviations: SOD-1, super oxide dismutase-1 mutation; RCT, randomized, controlled trial.

Francisco. The levels of evidence were graded as 1a-c, 2a-c, 3a-b, 4, and 5.⁵⁵

Operational Definitions and Evidence-Based Calculations

To determine improvement, the absolute benefit, and relative difference in the change score from baseline to post-treatment were calculated.⁶³ Specifically, the absolute benefit was calculated as the difference in mean change scores in the treatment group versus the control group. Relative benefit was calculated as the absolute benefit divided by the baseline mean of the intervention and control groups. To determine whether the difference observed in each outcome measure constituted a clinically important change, we compared the relative benefit to the minimal clinically important difference (MCID), which is defined as the smallest differ-

TABLE 6. Levels of Evidence According to Sackett et al⁵⁵

Level of Evidence	Therapy/Prevention/Etiology/Harm
1a	Systematic review with homogeneity of RCTs
1b	Individual RCT with narrow confidence intervals
1c	All or none
2a	Systematic review with homogeneity of cohort studies
2b	Individual cohort study (including low-quality RCT, eg, <80% follow-up)
3a	Systematic review (with homogeneity) of case-control study
3b	Individual case-control study
4	Case series and poor-quality cohort and case-control studies
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"

ence in a score that is considered worthwhile or important.⁶⁴ The MCID for each measure was determined by a review of available literature.

- When data were available, calculations for treatment effects were performed based on common definitions and instructions.⁶⁵
- *Control Event Rate*: The proportion of participants in the control group in whom an event is observed.
- *Experimental Event Rate*: The proportion of participants in the experimental (intervention) group in whom an event is observed.
- *Relative Risk Reduction*: The proportional reduction in rates of bad outcomes between experimental (intervention) and control participants in a trial.
- *Absolute Risk Reduction*: The absolute arithmetic difference in rates of bad outcomes between experimental (intervention) and control participants in a trial.
- *Number Needed to Treat*: The number of subjects who need to be treated to achieve one additional favorable outcome.

Calculations were based on a 2×2 χ^2 table. For each outcome measure, a critical value based on the researcher's assessment of a clinically important change was assigned. The frequency of scores under the critical values, representing adverse outcomes, was then determined for each treatment group. Similarly, the frequency of scores above the critical value, reflecting a favorable outcome, was determined for each treatment group. The theoretical calculations are summarized in Figure 1.

Effect sizes for each study were analyzed when data were available to determine the mean difference scores (baseline to postintervention) divided by the standard deviation of the change score. The mean weighted effect size was also calculated across studies. The data points in Figures 2–4 represent the effect sizes between two groups when compared for a specific outcome. The horizontal lines represent the standard deviations for each measure.

In the animal studies, to determine improvement, the absolute and relative differences in life span were calculated. The absolute benefit was calculated as the difference in means for the treatment groups minus the means for the control groups. Relative difference was calculated as the absolute benefit divided by the mean of the control group.⁶³

To determine the life span and motor function outcomes described in the animal studies, linear curves for the intervention and control groups were plotted. These curves were constructed by averaging 0%, 25%, 50%, 75%, and 100% life-span time and motor function data for each experimental group for each study. The average of these data was then plotted on separate linear curve graphs. The MCID for each measure for the animal model was determined by a review of the available literature.

Assessing the Validity, Importance, and Applicability of the Evidence

To answer the question "are the results of this individual study valid?," Sackett et al⁵⁵ identifies the following three questions as the most important to answer: (1) Was the

A Control Group		B Experimental Group	
Adverse Event	No Adverse Event	Adverse Event	No Adverse Event
Pre	A	B	
Post	C	D	

Calculations:

Control Event Rate (CER) = $A / A + B - D / C + D$
 Experimental Event Rate (EER) = $a / a + b - d / c + d$
 Relative Risk Reduction (RRR) = $EER - CER / CER$
 Relative Risk Increase (RRI) = $EER - CER / CER$
 Absolute Risk Reduction (ARR) = $EER - CER$
 Absolute Risk Increase (ARI) = $EER - CER$
 Number Needed to Treat (NNT) = $1 / ARR$
 Number Needed to Harm (NNH) = $1 / ARI$

FIGURE 1. Model for calculating evidence-based statistics. These statistics were applied to the studies to determine the value of the evidence.

assignment to group randomized? Was the randomization list concealed? (2) Was follow-up of participants sufficiently long and complete? and (3) Were all the participants analyzed in the groups to which they were assigned? To address the importance of each therapeutic study, Sackett et al⁵⁶ recommend assessing research via two questions: (1) What is the magnitude of the treatment effect? and (2) How precise is this estimate of the treatment effect? Finally, to determine the applicability of the results of intervention studies, Sackett et al⁵⁵ suggest using the following questions: (1) Are our patients so different from those in the study that its results cannot apply? (2) Is the treatment feasible in our setting? (3) What are our patients' potential benefits and harms from the therapy? and (4) What are our patients' values and expectations for both the outcome that we are trying to prevent and the treatment that we are offering?⁵⁵ This method of analysis was applied to the human studies included in this review. Although Sackett et al⁵⁵ do not make specific provisions for assessing the validity of animal studies, the same analysis was applied to the experimental animal studies.

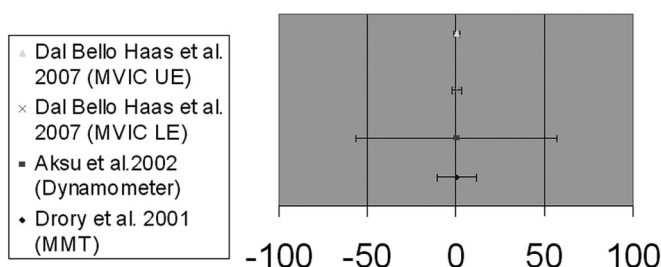
Effect size: strength measurement

FIGURE 2. Effect size for strength in human studies. Strengthening exercises were not associated with improvement or reduction in strength.

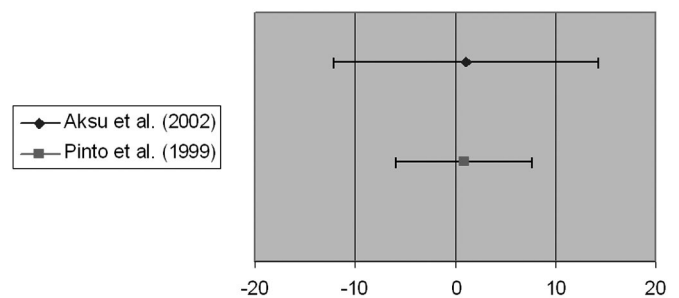
Effect Size: Norris ALS Scale

FIGURE 3. Effect size for Norris amyotrophic lateral sclerosis scores in human studies. The benefits of the exercise programs were negligible, but participants were not worse, as measured by the Norris amyotrophic lateral sclerosis score.

RESULTS**Search Results**

The results of the evidence-based search for human and animal studies are summarized in Table 7. In PubMed alone, *exercise and ALS* produced 62 citations, 1979–2008. Of these publications, the majority were appropriate to provide background information about the pathology, medical management, and general physical therapy for persons with ALS. Fifteen were not pertinent to ALS. Nine clinical studies and five animal studies specifically addressed the effects of exercise and ALS. One article outlined the protocol to use for a systematic review of exercise and ALS and was not considered appropriate to answer the primary question.⁶⁶ Three studies were excluded as summarized in Table 8. One systematic review and four prospective clinical trials with human subjects remained. One study was a nonblinded, noncontrolled, and nonrandomized study.⁶⁷ Another was a nonblinded, controlled study with random assignment.⁶⁸ Two studies were single-blinded, randomized controlled trials.^{69,70} The two studies included in the systematic review had already been selected for review within the prospective, controlled studies.^{69,70} Table 9 summarizes the four clinical studies and one systematic review included to answer the primary question.

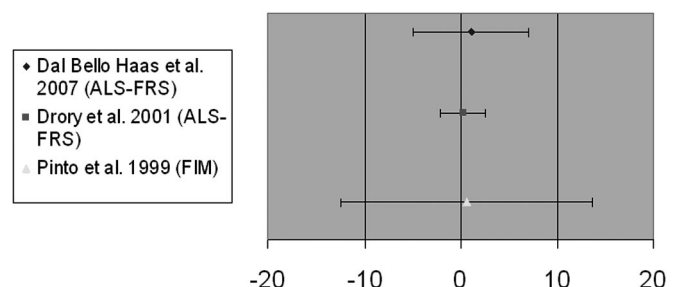
Effect size - functional scores

FIGURE 4. Effect size for functional scores in human studies. Exercise programs were not associated with decreased or increased functional scores.

TABLE 7. Summary of Evidence-Based Search

Type of Study	Human Studies	Animal Studies
Meta-analyses/systematic reviews	1*	0
RCT	2	4
Prospective clinical trials	2	0
Case study	0	Not Applicable

After exclusions, a total of five human studies and four animal studies met the criteria for this evidence-based search.
* Included two studies already included in the evidence-based search

TABLE 8. Human Studies Not Included in Evidence-Based Review^{45,53,90}

Study	Reason Excluded
Lenman ⁹⁰	Unclear diagnosis, insufficient information on exercise, follow-up, and outcome measures
Bohannon ⁵³	Case report with insufficient follow-up and outcome measures
Dal Bello-Haas ⁴⁵	Unclear exercise intervention, no baseline vs intervention measurement

After reviewing the complete studies, three clinical studies were excluded.

The results of the evidence-based search for animal studies are summarized in Table 10. The search did not yield any systematic reviews but did produce five randomized controlled trials using the SOD-1 transgenic mouse model.^{71–75} One study was excluded because of insufficient data for evidence-based calculations with respect to survival time and motor function,⁷¹ leaving four studies to analyze to answer the primary question.

TABLE 9. Summary of Human Studies Included in Evidence-Based Review

Study	Study Design	Description	No. Subjects	Level of Evidence	Outcome Measures
Aksu et al ⁶⁷	Prospective; convenience assignment to groups	Supervised (PNF + strength) and HEP (stretching/ROM) for 45–60 min, 3 times per week × 8 wks vs HEP only, “as tolerated”	26	3b	Norris ALS score Strength (dynamometer)
Drory et al ⁶⁹	Prospective controlled; random assignment	Moderate load active exercise, 2–15 min bouts per day for up to 6 months vs no additional activities besides daily routine (control)	25	2b	ALS-FRS Strength (MMT) FSS
Pinto et al ⁶⁸	Prospective controlled; random assignment	Treadmill with BiPAP (no frequency specified, for up to 12 months) vs control (no additional activities besides daily routine) with BiPAP	20	2b	Norris ALS FIM FVC
Dal Bello-Haas et al ⁷⁰	Randomized clinical trial	Resistance exercise group had significantly higher ALSFRS and FSS and no adverse effects	27	2b	ALS FRS, FSS
Dal Bello-Hass et al ⁷⁸	Systematic review*	At 3 months, the risk ratio was 3.32 for ALSFRS (three times higher for exercise group) and –6.35 for FSS (six times better for the exercise group)	(52)	1b	ALS FRS, FSS

Four clinical studies and one systematic review met the criteria for this review and provided evidence to answer the primary questions.
* Using data from the Drory et al⁶⁹ and Dal Bello-Haas et al⁷⁰ studies.
Abbreviations: PNF, proprioceptive neuromuscular facilitation; HEP, home exercise program; ALS-FRS, amyotrophic lateral sclerosis functional rating scale; MMT, manual muscle testing; BiPAP, biphasic positive airway pressure; FIM, functional independence measure; FVC, forced vital capacity.

The levels of evidence ranged from 1b to 5. The highest level of evidence was 1b (small systematic review).⁷⁸ The next highest level of evidence was 2a (the two small randomized, clinical trials that were included in the systematic review).^{69,70} Next were a prospective controlled study (2b) by Pinto et al,⁶⁸ and a cohort study with assignment to treatment by convenience (3b) by Aksu et al.⁶⁷ All the animal studies received a grade of 5 for their clinical importance to humans per the guidelines of Sackett et al,⁵⁵ even though all of the animal studies represented blinded, randomized controlled trials. Thus, the average level of evidence for all nine of the studies was 3.3. The average level of evidence for the clinical studies was 2.5.

Study Findings
Human Studies

The first study was a randomized clinical trial by Dal Bello-Haas et al,⁷⁰ which included 27 participants with ALS who were randomly assigned to either a usual care program (n = 14) or a resistance training program (n = 13). Eight participants (60% of participants) in the exercise resistance group completed the program, whereas 10 participants (75% of participants) in the usual care group completed the study. Participants performing the resistance program achieved a relative benefit of 17.7% in upper extremity strength and 14.4% in lower extremity strength compared with controls (Table 11). Participants in the exercise group also showed a relative benefit of 11.9% on the ALS-FRS (included in the analysis above) and 11% on the FVC compared with controls (Tables 13 and 14, respectively). This level of relative benefit represents a clinically important change in ALS-FRS, given that previous studies have reported that a difference of 7.5%

TABLE 10. Summary of Animal Studies Included in Review

Study	Study Design	Description	Level of Evidence	Outcome Measures
Kaspar et al ⁷²	RCT	Running wheel (daily): 2, 6, or ad lib (12 h) access	5	Rotarod test survival time
Liebetanz et al ⁷³	RCT	Running wheel: 400 min/day, 7 times per week at 3.4 or 0.1 m/min	5	Survival time motor symptoms (grip strength, stride length, tight rope test)
Mahoney et al ⁷⁴	RCT	Treadmill: 20–45 min, 3–5 times per week at 9–22 m/min	5	Survival time clinical symptoms grading scale Rotarod beam
Kirkinezos et al ⁷⁵	RCT	Treadmill: 30 min, 5 times per week at 13 m/min	5	Survival time

Five animal studies were located for the review but one animal study was excluded because there was insufficient survival time and motor function data.⁷¹
Abbreviations: RCT, randomized controlled trial.

on the ALS-FRS may be considered clinically significant.⁷⁶ However, the observed change in FVC may not be clinically important, as studies have established the MCID as 20% for FVC.⁷⁷ The effect sizes were moderate (0.42–0.58) for upper and lower extremity strength (Fig. 2) and large for ALS-FRS (1.06, Fig. 4) and FVC (1.2, Fig. 5). The intent-to-treat model was not used and those dropping out were lost to follow-up.

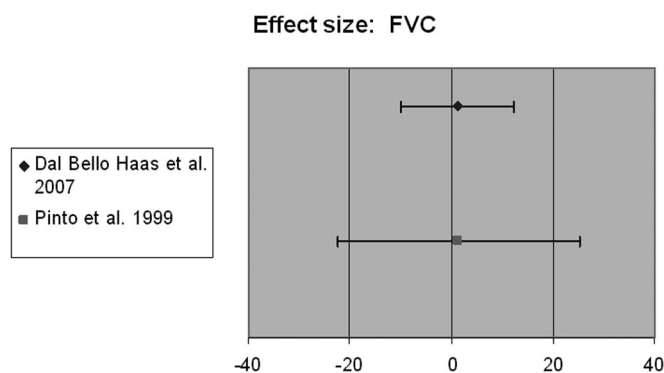


FIGURE 5. Treatment effects for forced vital capacity. Exercise was associated with a slight improvement in vital capacity.

Thus, it was not possible to determine the outcomes for those who did not complete the study.

The second study, by Aksu et al,⁶⁷ evaluated the effects on muscle strength and functional level using a supervised and a home exercise program compared with a home exercise program only. In this experimental study, 26 participants with ALS were assigned by convenience to the treatment groups, to assure each group had 13 participants. The investigators were not blinded to the treatment groups. After six months, strength was assessed by using a hand-held dynamometer and disease severity/functional level was assessed by the Norris ALS Scale (see summary in Tables 11 and 12, respectively). Participants performing the supervised and the home exercise program demonstrated a relative benefit in strength of 18.4% and a relative benefit on the Norris ALS Scale of 41.3% compared with participants performing the home program alone. It is difficult to determine if these differences are clinically important because no studies describing MCIDs for hand-held dynamometry or the Norris ALS Scale were found. However, the relative benefit in strength data reflects an improvement of 7–10 kg of force, averaged across 34 muscle groups tested. The effect sizes between the two treatment groups were 0.372 in favor of the supervised and home program for strength and 1.11 in favor of the supervised plus

TABLE 11. Benefits in Strength in Human Studies

Study	Outcome	Experimental Group	Baseline Mean	End of Study Mean	% Change Score	Relative Risk Reduction	Risk Ratio
Aksu et al ⁶⁷	Isometric strength (dynamometer)	Supervised exercise + Home exercise (13)	334.7 ± 150.2 kg	343.5 ± 155.9 kg	8.74 kg (2.6%)	84.5%	6.46
		Home exercise only (13)	286.7 ± 155.8 kg	238.4 ± 151.0 kg	-48.3 kg (-16.8%)		
Drory et al ⁶⁹	Manual muscle testing	Exercise (14)	85 ± 10	80 ± 20	-5.0 (-5.9%)	66.5%	2.98
		Control (14)	85 ± 4	70 ± 40	-15 (-17.6%)		
Dal Bello-Haas et al ⁷⁰	MVIC upper extremity	Exercise (13)	-9.8 ± 4.6	-10.1 ± 5.0	-1.1 (-11.6%)	18.0%	1.3
		Control (14)	-8.3 ± 3.6	-10.2 ± 2.8	-1.9 (-22.9%)		
Dal Bello-Haas et al ⁷⁰	MVIC lower extremity	Exercise (13)	-20 ± 3.8	-19.7 ± 8.2	2.3 (11.5%)	10.0%	1.05
		Control (14)	-23.1 ± 4.8	-25.9 ± 5.0	2.8 (-12.1%)		
MWD		87 subjects				54.1%	3.62

Dal Bello-Haas et al⁷⁰ found relative benefits of 17.7% and 14.4% for UE and LE strength, respectively, using maximum voluntary isometric contraction testing after 6 months of resistance training (n = 8) compared to nonexercising controls (n = 10). Aksu et al⁶⁷ found an 18.35% relative improvement in cumulative isometric strength for 34 muscles tested after eight weeks of supervised exercise plus home program (n = 13) compared to home program alone (n = 13). Drory et al⁶⁹ found a 13.95% relative improvement in cumulative manual muscle testing of 20 muscles after six months of exercise (n = 14) compared with nonexercising controls (n = 11). The MCIDs have not been established for these measures.

Abbreviations: MVIC, maximum voluntary isometric contraction.

TABLE 12. Benefits in Norris ALS Scores in Human Studies

Study	Outcome	Experimental Group	Baseline Mean	End of Study Mean	% Change Score	Relative Risk Reduction	Risk Ratio
Aksu et al ⁶⁷	Norris scale	Exercise (13)	33.9 ± 15.6	30.81 ± 9.89	−3.1 (−9.1%)	81.9%	6.22
		Control (13)	30.1 ± 14.1	13.75 ± 8.03	−17.1 (−56.6%)		
Pinto et al ⁶⁸	Norris scale	Exercise (13)	41.3 ± 3.0	36.6 ± 6.8	−4.7 (−11.4%)	59.0%	2.44
		Control (14)	37.6 ± 7	26.8 ± 10.6	−10.8 (−27.8%)		
MWD		53 subjects				70.7%	4.29

Aksu et al⁶⁷ found a 41.3% relative improvement on total Norris ALS scores after one year of follow up in patients who performed a supervised exercise plus home program (n = 13) compared to home program alone (n = 13). Pinto et al⁶⁸ found a 15.5% relative improvement on total Norris scores after six months of exercise (n = 14) compared to non-exercising controls (n = 11). The MCID of the Norris ALS score has not been established.

home program for the Norris ALS Scale (see Figs. 2 and 3, respectively). Although the effect size for strength gains was small, the effect size for the Norris ALS Scale was large, both favoring the supervised plus home exercise group over the home exercise only group. There was insufficient information to determine the benefits based on the calculation of treatment effect (CER and EER) as described by Sackett et al.⁵⁵

The third study by Drory et al⁶⁹ examined the effect of daily moderate-load active exercise compared with no additional activities. In this small randomized clinical trial, 25 participants were randomly assigned to exercise (n = 14) or control (n = 11) group. The investigators were not blinded to treatment groups. Every three months for a six-month period, strength was assessed by MMT, and function was assessed with the ALS-FRS (see Table 11). The exercise group experienced a 13.95% relative benefit in strength compared with the control group. The risk ratio was 2.98 (almost three times less decrease in strength in the exercise group compared with the control group). MCIDs have not been established for MMT measures, making it difficult to interpret the clinical significance of this change. However, this relative benefit corresponds to a difference of between one-half grade and one full grade on a manual muscle test averaged over 20 muscle groups. Exercising participants also showed a relative benefit of 9.1% on ALS-FRS scores compared with nonexercising controls (Table 13). This may represent a clinically important change, because it has been suggested that a difference of 7.5% on the ALS-FRS is clinically significant.⁷⁶

Comparison of the effect sizes between treatment groups revealed results in favor of the exercise group for both strength (0.343, Fig. 2) and functional score (0.208, Fig. 4). These effect sizes are considered small. There was insufficient information to determine treatment effects as described by Sackett et al.⁵⁶

In the fourth study, Pinto et al⁶⁸ presented data comparing disease progression in breathing with biphasic positive airway pressure (BiPAP). Using a prospective experimental design, 20 consecutive participants with ALS were assigned to exercise (n = 8) or control (n = 12) group. Investigators were blinded to treatment group in this study. Disease progression was measured by change in respiratory function using FVC, and functional scores, including the Norris ALS Scale and FIM. Measurements were taken every three months for twelve months. The exercise group demonstrated improved outcomes compared with the control group. Participants performing treadmill exercise showed relative risk benefits of 15.5% on the Norris ALS Scale (Table 12), 10.2% on FIM scores (Table 13), and 28.6% on FVC (Table 14). As noted previously, the MCID for the Norris ALS Scale has not been established, making it difficult to interpret the clinical importance of this relative benefit. The MCID for the FIM is reported to vary between 6.8% and 10.6% (11–17 points in raw scores)⁶⁴; thus the relative benefit of 10.2% likely represents a clinically important improvement in function. Similarly, a difference of >20% in FVC is considered clinically important.⁷⁷ Therefore, the reported relative benefit of 28.6%

TABLE 13. Benefits in Functional Scores in Human Studies

Study	Outcome	Experimental Group	Baseline Mean	End of Study Mean	% Mean Change	Relative Risk Reduction	Risk Ratio
Drory et al ⁶⁹	ALS-FRS	Exercise (14)	29 ± 4	28 ± 4.5	−1.0 (−3.4%)	9.1%	3.97
		Control (14)	26 ± 3	22.5 ± 10	−3.5 (−13.5%)		
Dal Bello-Haas et al ⁷⁰	ALS-FRS	Exercise (13)	35.2 ± 3.6	33.8 ± 4.7	−1.4 (−4.0%)	75.6%	4.1
		Control (14)	33.6 ± 2.4	28.1 ± 4.8	−5.5 (−16.4%)		
Pinto et al ⁶⁸	FIM	Exercise (14)	118.4 ± 6.3	102.1 ± 18.6	−16.3 (−13.8%)	39.1%	1.89
		Control (12)	106.6 ± 22.6	78.8 ± 26	−27.8 (−26.1%)		
MWD		87 subjects				29.5%	3.12

Dal Bello-Haas et al⁷⁰ found a relative improvement of 11.9% on total ALS-FRS scores for patients performing 6 months of resistance exercises (n = 8) compared with non-exercising controls (n = 10). Drory et al⁶⁹ reported a 9.1% relative improvement on total ALS-FRS scores after six months of exercise (n = 14) compared to non exercising controls (n = 11). The MCID for the ALS-FRS corresponds to a change of 7.5%. Pinto et al⁶⁸ found a 10.2% relative improvement on total FIM scores after 12 months of exercise (n = 8) compared to non-exercising controls (n = 12). The MCID for FIM scores has been shown to vary between 6.8 and 10.6%.

Abbreviations: ALS-FRS, amyotrophic lateral sclerosis functional rating scale; FIM, functional independence measure.

TABLE 14. Benefits in Respiratory Function in Human Studies

Study	Outcome	Experimental Group	Baseline Mean	End of Study Mean	Mean % Change Score	Relative Risk Reduction	Risk Ratio
Pinto et al ⁶⁸	FVC (% predicted)	Exercise	76 ± 0.20	60 ± 0.20	−16 (−25%)	39.6%	1.66
		Control	99 ± 0.15	58 ± 0.17	−41 (41.4%)		

Dal Bello-Haas et al⁷⁰ reported 11% relative improvement in patients performing 6 months of resistance training (n = 8) vs controls (n = 10). Pinto et al⁶⁸ found a 28.6% relative improvement on FVC measures after 12 months of exercise (n = 8) compared to nonexercising controls (n = 12). The MCID for FVC measurement is 20%.
Abbreviation: FVC, forced vital capacity.

likely represents a clinically important improvement in respiratory function. The effect sizes were also large, 0.89, 0.63, and 2.39, respectively, in favor of the treatment group for the Norris ALS Scale, the FIM scores, and the FVC (see Figs. 3–5).

The treatment effects for the Norris ALS Scale, FIM, and FVC measurements in the study by Pinto et al⁶⁸ are summarized in Figures 6–8, respectively. Using the Norris ALS Scale, exercise decreased the relative risk of disease progression by 100% and the absolute risk by 25%. As measured by the FIM, exercise decreased the relative risk of functional loss by 50% and the absolute risk by 25%. Four participants would need to participate in an exercise program for one additional participant to benefit by 25% as measured by the Norris ALS Scale and the FIM. Exercise decreased the relative risk of worsened respiratory function by 12.5% and the absolute risk by 4%. Twenty-four subjects would need to participate in an exercise program for one additional subject to experience a worsening of respiratory function.

The Cochrane Collaboration systematic review by Dal Bello-Haas et al⁷⁸ included studies from January 1980 to August 2007. This review included only randomized clinical studies of participants with definite, probable, probable with laboratory support, or possible ALS defined by the El Escorial criteria.⁷⁸ Exercise programs included progressive resistance or strengthening and endurance or aerobic exercise. No exercise participation or usual activities were the control for the standard condition. Only two randomized clinical trials met the criteria for inclusion; these trials, by Dal Bello-Haas et al⁷⁸ and Drory et al,⁷⁰ have also been included in this evidence-based review, as described above.

In the systematic review, Dal Bello-Haas et al,⁷⁸ calculated the mean weighted difference scores for the ALS-FRS from the two randomized clinical trials studying the benefits of therapeutic exercise for persons with ALS. After

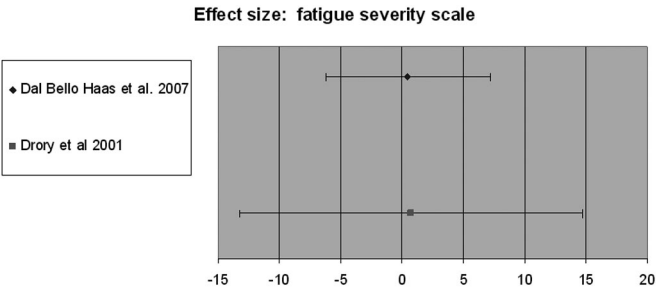


FIGURE 6. Treatment effects for fatigue. Exercise was associated with a moderately strong benefit in fatigue reduction.

three months, the difference of the mean weighted relative risk on the ALS-FRS was 3.32 (95% CI, 0.56–5.96) in favor of the exercise group. Those participating in exercise were three times more likely to improve in function compared with those in the usual care group. With an absolute risk reduction calculated at 3.91, only one more participant would need to be treated with the exercise program for three months for one more participant to experience a decrease in the ALS-FRS score by 10%. At three months, the usual care group decreased function by more than six times compared with the exercise group. However, there were no statistically significant differences in the measurements of quality of life, fatigue, or muscle strength between the exercise and the usual care groups. Based on this analysis of ALS-FRS, the conclusion was that the studies were too small to determine the extent to which strengthening exercises are beneficial or harmful for persons with ALS. These conclusions⁷⁸ mirrored the findings for this evidence-based review as noted above.

Integration of Findings for Human Studies

The criteria recommended by Sackett et al⁵⁵ were applied to assess the validity, importance, and applicability of these studies. Only one of the human studies met all of the criteria for valid intervention research (systematic review, 1b).⁷⁸ The other studies were classified as 2b to 3b. The common outcomes of the studies of Dal Bello-Haas et al⁷⁰ and Drory et al⁶⁹ were averaged within the Cochrane Review, with the other individual outcomes presented under separate analysis. Based on Sackett et al,⁵⁵ the effect sizes on the

Exercise Group (n=8)		Control Group (n=12)	
Norris<25	Norris>26	Norris<25	Norris>26
Pre	0 8	Pre	1 11
Post	0 8	Post	4 8

- Critical value was 25 (Score of less than or equal to Trace [1] for each item); adverse event defined as score at or below this
- EER = 0 - 0 = 0 %
- CER = 4/12 - 1/12 = 25%
- RRR = |EER - CER| / CER = 100%
- ARR = |EER - CER| = 25%
- NNT = 1 / ARR = 4

FIGURE 7. Treatment effects for Norris amyotrophic lateral sclerosis scores.

Exercise Group (n=8)			Control Group (n=12)		
	FIM < 92	FIM >93		FIM < 92	FIM >93
Pre	0	8	Pre	3	9
Post	2	6	Post	9	3

- Critical value was 92 (Score of less than or equal to 4 [modified requiring minimal assistance] for each item); adverse event defined as score at or below this
- EER = $2/8 - 0/8 = 25\%$
- CER = $9/12 - 3/12 = 50\%$
- RRR = $1 \text{ EER} - \text{CER} = 25\%$
- ARR = $1 \text{ EER} - \text{CER} = 25\%$
- NNT = $1 / \text{ARR} = 4$

FIGURE 8. Treatment effects for functional independence measure scores. Four individuals would need to be treated with exercise for one more individual with ALS to benefit with respect to function.

ALS-FRS varied from small to large. Overall, only one more participant would need to be treated to have one more participant experience an increase in the ALF-FRS score. However, this gain in function was only measured up to three months after initiation of exercise.

When outcomes were averaged across measurements from all four human studies, small to large effect sizes of 0.208 to 1.39 were measured for each of the dependent variables. The mean weighted risk ratios across all four studies were three times higher in favor of the exercise group for maintained strength (MWD risk ratio, 3.62), maintained performance on the Norris ALS Scale (MWD risk ratio, 4.3), and function (MWD risk ratio, 3.12). The mean weighted effect size for maintenance of respiratory function was also high (mean weighted effect size, 1.2–1.39), and the risk ratio was 1.66% better than chance alone for exercise to improve respiratory function in persons with ALS. Based on the evidence of this review, there were benefits associated with exercise compared with nonexercising controls. In addition, there were no measurable harms reported with the exercise programs in terms of ALS disease progression.

The methods recommended by Sackett et al⁵⁵ were then applied to determine the applicability of the findings in these studies. ALS is a relatively rare disease, the number of participants in any one study is small, and there is a heterogeneous clinical presentation and disease progression. Thus, most clinical trials were not able to include a large representative sample of participants with ALS. This leads to larger variations in measurements, which can compromise detection of true differences between control and experimental groups.³⁰ Furthermore, Armon⁷⁹ raised concerns about the Dal Bello-Haas⁷⁰ study in that the progression rate for the usual care group was higher than for the exercise group. Also, Armon⁷⁹ noted that the FVC for the participants in the exercise group was unusually high, which raises questions about the safety of strengthening exercises in persons with decreased FVC. For example, in the study by Pinto et al,⁶⁸ participants had compromised FVC and needed to use BiPAP to complete the exercise program.

On the other hand, based on available diagnostic criteria, the participants in these studies were comparable with those who would commonly be encountered in any outpatient setting for persons with ALS. Furthermore, the exercise interventions used in the human studies were feasible: the exercise programs required no special equipment and could be performed in any setting. However, patients with respiratory compromise had to complete their exercise program while using BiPAP in the study by Pinto et al.⁶⁸ Based on previous investigations and the studies included in this review, the participants with ALS achieved a variety of benefits from the exercise programs (ie, maintenance of strength, respiratory capacity, and function). Dal Bello-Haas et al⁷⁰ indicated that gains from exercise were no longer apparent three months after exercise; however, no harm (eg, loss of energy, decreased participation in other activities, disease progression) from exercise was reported.

There were several limitations in the human studies reviewed. First, the studies did not routinely include random selection, random assignment to treatment, or blinding of investigators. Second, follow-up of the participants was not always long term, and most did not follow the intent-to-treat model. Third, all studies reviewed had relatively small sample sizes, decreasing their statistical power, and one study⁶⁷ did not have a complete or long-term follow-up and lacked a control group. Fourth, the study by Pinto et al⁶⁸ described significant pretreatment differences between exercise and control groups. Fifth, the studies varied in the exercise modalities and protocols (eg, frequency, load, duration) used, and only one study differentiated the exercise program based on muscle strength assessment; the studies also varied in the dependent measures used to determine disease progression. This limited comparison of results from the different studies. Sixth, each study reported large standard deviations and consequently wide 95% CIs for each dependent measure, which limits the significance of the effect sizes observed. Seventh, participants required use of BiPAP when completing cardiovascular exercise; some persons may not have access to a portable BiPAP machine (sometimes due to insurance limitations) and therefore would not be able to complete this protocol. In addition, it may be awkward to exercise while using a BiPAP machine or a portable respirator, although generally the units can be attached to a stationary bike, a treadmill, or a walker. Eighth, the study by Dal Bello-Haas et al⁷⁰ included only participants with FVC $\geq 90\%$ and ALS-FRS ≥ 30 ; as such, these results may not be generalizable to persons with more respiratory and functional compromise (ie, in later stages of the disease).

Animal Studies

All animal studies included where randomized clinical trials with emphasis on a mouse model of ALS. The study by Kaspar et al⁷² studied the effects of exercise duration and the synergism of these effects with IGF-1 gene therapy on SOD-1 transgenic mice. Seventy-two mice were randomly assigned to one of four treatment groups ($n = 18$ for each group), including a control group that only performed usual activities, and three exercise groups that were given access to a running wheel for 2, 6, or 12 hours per day. Outcome measures

included survival time and motor function as assessed by an accelerating Rota-rod test. Because this review focused on exercise interventions, data based on the IGF-1 gene therapy intervention were not included in the calculations. Compared with controls, analysis showed that short duration exercise (two hours per day) group had a 7% absolute increase in survival time and a relative increase in survival of 5.55%. The moderate duration (six hours per day) group demonstrated a 40.5% absolute increase and a 28.4% relative improvement in survival time compared with controls. The long duration (12 hours per day) group had a 24.5% absolute improvement and an 18.18% relative increase in survival time.

Liebetanz et al⁷³ studied the effects of vigorous physical activity using a motorized running wheel in SOD-1 transgenic mice compared with less-exercised and nonexercised transgenic mice. Thirty-seven mice were randomly assigned to one of three treatment groups: the control group ($n = 12$) did not perform exercise other than usual activities; the active mice ($n = 12$) ran for 400 minutes every day at 3.4 meters per minute (m/min); the sedentary group ran at 0.1 m/min for the same duration and frequency. Dependent measures included survival time and motor onset and progression disease, as assessed by grip strength, stride length, and tight rope test. The calculations for this study showed that the sedentary group had an absolute decrease of 1.9% and a relative decrease of 1.48% in survival time compared with the control group. In contrast, the active group demonstrated a 4.6% absolute increase and a 3.5% relative increase in survival time compared with the nonexercising control group.

The study of SOD-1 mice by Mahoney et al⁷⁴ examined the effects of high-intensity endurance exercise using a motorized treadmill. Thirty-nine mice were randomly assigned to two groups: the control group ($n = 25$) performed no additional exercise other than normal activities, whereas the high-intensity exercise group ($n = 14$) performed a progressive treadmill program four to five times per week, which varied from 20 to 45 minutes each session and from 9 to 22 m/min, depending on the animals' tolerance. Outcome variables included disease onset (based on an eight-point clinical rating scale that assessed muscle strength and abnormal reflexes), motor performance (assessed by an accelerating Rota-rod beam), and disease progression (survival). Analysis revealed that mice exercising at an intense level had an absolute decrease of 3% and a relative decrease of 2.28% in survival time compared with nonexercising control mice.

Kirkinezos et al⁷⁵ evaluated the effects of regular exercise on the progression of ALS in SOD-1 mice using a motorized treadmill program. Sixty mice were assigned to either a nonexercising control group ($n = 30$) or an exercise group ($n = 30$), which included running 13 m/min for 30 minutes five times per week. The only outcome measure for this study was survival time. Analysis of these data revealed that the exercising SOD-1 mice experienced an 8.5% absolute increase and a 6.19% relative increase in life-span compared with nonexercising control mice.

Integration of Findings Across Animal Studies

Table 15 summarizes the mean differences, risk ratios and effect size for the exercise intervention groups compared

with controls for all of the animal studies included in this review. Figure 8 shows the combined survival curves for life span averaged over all animal studies. When averaged together, the results from these animal studies showed that the median life span for SOD-1 mice increased from a baseline of 122 to 133 days for the control groups and from 127 to 147 days for the exercise groups (Fig. 8). In addition, the time to reach a 50% decline (eg, median level) in motor function was 115 days for the control groups, compared with 122 days for the exercise groups (Fig. 9). The mean weighted difference in survival was 11.3% in favor of the exercise group.

When examined individually, the effects of exercise on survival time varied in the animal studies. The study by Kaspar et al⁷² showed a positive risk ratio in favor of exercise for increased life span for all groups undergoing self-paced exercise. Likewise, the study by Kirkinezos et al⁷⁵ reported a positive effect on life span for the exercise group using a moderate treadmill program. In contrast, the study by Liebetanz et al⁷³ showed a positive risk ratio in favor of faster (ie, more intense) treadmill exercise but a negative risk ratio for slower (ie, less intense) treadmill exercise with respect to survival time. The study by Mahoney et al⁷⁴ showed a negative risk ratio against vigorous treadmill exercise, which shortened mean survival time by three days. The mean weighted average risk ratio was not significantly different than chance alone supporting the benefit of exercise (0.80).

The effect sizes were calculated for three of the four studies. Again, the studies by Kaspar et al⁷² and Kirkinezos et al⁷⁵ reported moderate to large positive effect sizes in support of the benefit of exercise. Liebetanz et al⁷³ reported a moderate positive effect size in favor of faster (ie, more intense) exercise, but a small negative effect size of slow (ie, less intense) exercise in terms of survival time. The study by Mahoney et al⁷⁴ showed a small to moderate negative effect size against exercise. The mean weighted effect size was 1.39 in favor of exercise (Table 15, Figs. 10 and 11).

The programs used in the animal studies varied in exercise modality, frequency, duration, and intensity in the animal studies. The most favorable outcomes in terms of improved life span were associated with a self-paced running wheel exercise program for 2 to 12 hours/day or a moderate treadmill exercise program (3.4–13 m/min) for 0.5 to 6.7 hours.^{73,75} The negative effects on life span were associated with high-intensity exercise to tolerance (9–22 m/min for 20–45 minutes daily) or slow rate exercise (0.1 m/min) for 6.7 hours a day; this latter regimen constituted less activity than the amount of exercise performed by the animals in usual unrestricted activities.

There are no published data on MCIDs for life span or motor function decline for the SOD-1 animal model of ALS. Thus, it is difficult to interpret these results with respect to clinical importance. The life expectancy for this strain of mice without any intervention is known to be 1.5 to 2 years for heterozygous (eg, not expressing SOD-1 mutation) mice and four to five months for homozygous (eg, expressing SOD-1 mutation) mice (J. Merriam, personal communication, January 2006, based on Gurney et al⁸⁰). Thus, exercise was associated with an increased life expectancy of approximately 11.3%.

TABLE 15. Differences in Survival Time in Animal Studies

Study	Experimental Group	Mean Survival Time (days)	Mean Difference Score	% Mean Difference	Risk Ratio	Effect Size
Kaspar et al ⁷²	Short ex (18)	129.5*	7	9.1	1.04	*
	Control (18)	122.5*				
Kaspar et al ⁷²	Mod ex (18)	163*	40.5	33.1	1.33	*
	Control (18)	122.5*				
Kaspar et al ⁷²	Long ex (18)	147*	24.5	20.0	1.2	*
	Control (18)	122.5*				
Liebetanz et al ⁷³	Slow ex (13)	127.2 ± 3.2	−1.9	−1.5	−0.98	−0.41
	Control (12)	129.1 ± 2.5				
Liebetanz et al ⁷³	Fast ex (13)	133.7 ± 3.2	4.6	3.6	1.04	1.14
	Control (12)	129.1 ± 2.5				
Mahoney et al ⁷⁴	Exercise (13)	130 ± 12	−3.0	−2.3	−0.98	−0.19
	Control (25)	133 ± 10				
Kirkinezos et al ⁷⁵	Exercise (30)	141.5 ± 2.5	8.5	6.4	1.06	2.6
	Control (30)	133 ± 2				
MWD	195 Exercise + control subjects			11.3	0.88	1.39

This table summarizes the changes in survival times of SOD-1 transgenic mice exposed to exercise compared to nonexercising controls. Absolute differences in survival times varied between a 3% decrease to a 40.5% increase in life span. Relative differences in survival times varied between a 2.3% reduction and a 33.1% improvement in life span. The MCID for survival time for this animal model has not been established. Total n, total of subjects in each of the exercise groups plus one control group/study; for effect size, n = 136.

* No standard deviation values available.

Abbreviations: Ex, exercise group.

When the criteria recommended by Sackett et al⁵⁵ were applied to evaluate the validity, importance, and applicability of the animal studies, no single animal study in this review met all of the criteria for validity. The studies were randomized clinical trials (levels 1b to 2a for human studies, but level 5 for animal studies). The effects were most often (two of three studies) in favor of a modest increase in survival for the low to moderate-intensity exercise groups,^{72,75} although one study showed a small decrease in survival with lower intensity exercise.⁷³ With higher intensity exercise, one study found a positive effect on survival,⁷⁴ whereas another found that survival decreased with vigorous treadmill exercise.⁷³ As

noted, the protocols used in these studies were not consistent with respect to exercise modality, intensity, frequency, or duration. In addition, it is not possible to directly translate the exercise protocols used in animal studies to human subjects. However, it seems that moderate exercise programs were more frequently associated with a positive effect on survival than high-intensity programs.

Despite the positive findings of moderate exercise from the animal studies, the applicability of animal studies to the management of ALS in humans remains debatable.³⁰ For example, the SOD-1 gene represents only one type of familial ALS (typifying 5–10% of persons with ALS).⁶ In addition, mice and humans have differences in terms of diet, cognition, emotion, aging, and disease, which interact with the application of findings.³⁰ For example, Riluzole is a glutamate

Exercise Group (n=8)		Control Group (n=12)	
FVC<50	FVC.50	FVC<50	FVC>50
Pre	1	7	
Post	4	4	

• Critical value was FVC = 50% (Mitsumoto 1998); adverse event defined as FVC < 50%
• EER = 4/8 – 1/8 = 37.5%
• CER = 4/12 – 0/12 = 33.3%
• RRI = | EER – CER | / CER = 12.5%
• ARI = | EER – CER | = 4.2%
• NNH = 1 / ARI = 24

FIGURE 9. Treatment effects for forced vital capacity. There were minimal differences between the experimental and control groups, suggesting no benefit or harm associated with exercise.

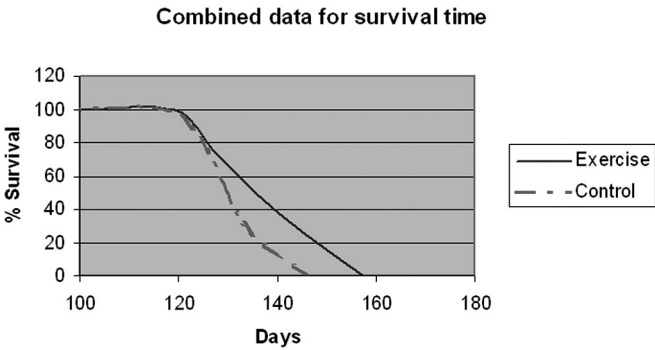


FIGURE 10. Combined survival curves for animal studies. The median life span for the exercise groups was increased by six days compared with the control groups (median life span = 130 days).

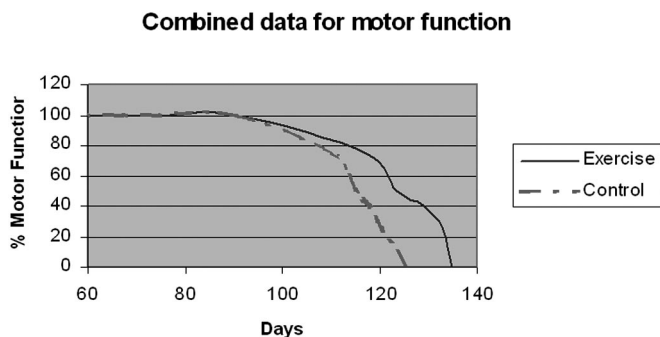


FIGURE 11. Combined data for change in motor function over time in animal studies. The time to reach 50% decline in motor function was 122 days for the exercise groups compared with 115 days for the control groups.

antagonist approved by the U.S. Food and Drug Administration to treat ALS. This drug has had dramatic effects on mice, but disappointing effects on humans.^{8,30} The same finding occurred for transactive response-DNA-binding protein 43, which was found in the individuals with neuronal inclusions of both ALS and ALSD frontotemporal dementia. TDP-re may be a means of distinguishing between SOD-1 and non-SOD-1 cases of ALS.⁸ As with the human studies, there were limitations of the reviewed animal studies. The most obvious limitation in the studies was the lack of blinding of investigators. In addition, as with the human studies, the animal studies lacked consistency in the exercise modality and protocol (eg, frequency, load or intensity, duration) used, making it difficult to draw comparisons between studies.

In summary, although animal models control many of the intrinsic and extrinsic factors threatening internal and external validity, exercise protocols used in animal studies cannot be translated 100% to those used for humans. On the other hand, the frequency, duration, and relative loads used in the animal studies could be used as a model for setting initial parameters of exercise training protocols for humans. Based on the studies included in this review, moderate exercise was more often associated with a slight increase in life span and delay in loss of motor function. The next step is to translate the findings from animal studies into randomized clinical trials.

DISCUSSION

The evidence-based search yielded five moderately strong human studies in terms of validity and importance, varying from 1b to 3b levels of evidence. The search also produced four animal studies that provided good basic scientific information about the effects of exercise in terms of survival in mice with SOD-1-induced ALS. Intervention studies between 1a and c levels of evidence are considered high-quality support⁵⁵ for or against a treatment (Table 6). Although by this definition, there was a paucity of high-quality randomized clinical trials involving human subjects examining exercise as an intervention strategy to improve function for persons with ALS, the findings of the studies reviewed were generally positive. There were no reported

adverse effects in any of the human studies; however, over time there was a large dropout rate. This was assumed to be due to the progression of the disease. The high-quality animal studies mostly reported benefits of moderate exercise in terms of enhancing life span, with some evidence that high-intensity exercise could compromise life span.

Based on this evidence, Hypothesis Ho 1 must be accepted and Ho 2 should be rejected. In small randomized clinical trials and experimental studies, exercise was associated with small to moderate, but not necessarily statistically significant, gains in function. However, neither the human studies nor the animal studies reported consistent adverse effects following moderate exercise. The benefits of different types of exercise protocols with respect to modality, frequency, intensity, or duration were not well differentiated. The studies using SOD-1 transgenic mice not only provided the most insightful information on survival, but also provided clear evidence that intense exercise could compromise life span.

At our university-based treatment center, persons with ALS vary in their expectations and values with respect to exercise. In general, immobilization has a negative effect on bone and muscle health.⁸¹ In addition, regular physical activity is generally considered a positive intervention, even for those with degenerative diseases.⁸² It is not surprising that a subset of persons with ALS consider exercise a valuable method of managing stress or a way to feel good. These individuals are reassured with reports that moderate exercise will not worsen their disease.

Most of the animal research studies suggest that moderate exercise may exert a neuroprotective effect on the neurophysiology of muscle contraction. This effect could occur by improving angiogenesis and astrocyte proliferation,^{83,84} enhancing blood vessel density,⁸⁵ increasing growth factors,⁸⁶ facilitating dendritic restructuring, increasing protein synthesis, improving axonal transport, avoiding over-stressing the fast twitch muscle fibers, and optimizing neuromuscular synaptic communication and electrophysiologic properties affecting neuronal gene expression.⁸⁷ In contrast, high-intensity exercise may damage mitochondria, increase extracellular edema damaging endothelial cell and basement membranes, increase oxidative stress,⁸⁸ and disrupt neurovascular units.⁸⁹

Adverse Effects

The adverse effects of exercise in ALS were not extensively discussed in the human studies included in this review. Pinto et al⁶⁸ reported that five of eight participants in the exercise group initially experienced oxygen desaturation with decreased end tidal volumes, but these participants were able to complete the study using more aggressive ventilatory assistance. It is not clear if true cardiovascular exercise at 70% maximum heart rate would be safe for persons with ALS, with or without respiratory support. In the study by Pinto et al,⁶⁸ one participant in the exercise group was unable to complete the exercise protocol and testing, but the authors did not describe or discuss this as an adverse event in this participant. Although Drory et al⁶⁹ reported a participant drop out rate of 68% within the first 6 months of the study, the

authors did not explain why participants dropped out of the study nor did they discuss any specific adverse events. This could suggest that the disease was progressing and the individuals could no longer participate in the exercise. One animal study reported that high-intensity exercise had an adverse effect on life span.⁷⁴ However, this study did not report on the specific histopathology surrounding this negative outcome.

Early investigations reported overuse atrophy and permanent loss of strength in persons with ALS who performed vigorous activities.⁴⁸ In addition, some persons with ALS report prolonged fatigue after overexertion. Taken together, increased fatigue could result in more disability even if impairment (ie, muscle strength and endurance) remained consistent. On the other hand, it is also possible that persons with ALS could maintain a high level of function despite impairment using exercise carefully matched to their physical ability (including speed of contractions and endurance).

In animal-based studies, researchers have examined possible adverse effects of exercise in terms of selective degeneration of motor neurons associated with excitotoxicity, increased calcium loads, or oxidative stress. In the study by Liebetanz et al,⁷³ mice were randomly assigned to run at high speeds, slow speeds, or be sedentary. Until 15 weeks, the animals showed minimal deterioration of motor function. At 20 weeks, all groups deteriorated in grip strength, stride length, and tight rope walking. Although there were no significant differences in survival time, the high exercise group had the longest mean survival time. These findings suggest that vigorous exercise might not always hasten motor neuron degeneration or disease progression.

Limitations of Search

One limitation of this evidence-based review was it only included studies available in English. Studies written in other languages might have provided higher levels of evidence. However, this evidence-based review was not funded, limiting opportunities to support translation services. Also, given the expense involved to obtain unusual documents, some databases were not included in the search, including EMBASE, LILACS, AMED, and HealthSTAR. As such, some high-quality studies may have been missed due to inaccessibility. Because of the low prevalence of ALS and the relatively short life span of persons with ALS, it is challenging to carry out randomized, controlled clinical trials. Another limitation is the constraint relative to integrating and translating basic science findings from animal-based models to clinical practice. Another concern is that the improved outcomes postexercise may be short lasting. For example, in the studies by Dal Bello-Haas⁷⁰ and Drory,⁶⁹ the benefits of the exercise group over the usual care groups were only measured up to three months post-exercise. However, these studies did not report on the benefits of continued, moderate-intensity exercise.

Gaps in Research and Recommendations for Future Studies

Further studies examining the benefits and risks of strengthening and aerobic exercise are warranted. Although

fatigue is known to limit function in persons with ALS¹¹ and can be used as a marker for disease progression,³² only two studies examined the effect of exercise on fatigue in the ALS population.^{69,70} In addition, each human and animal study in this review used different exercise protocols, and none of the studies specified modifications to exercise parameters based on participants' responses to exercise. As such, clinicians cannot directly use the results of these studies to guide exercise prescription for persons with ALS. Furthermore, the effects of exercise on disease progression in the context of the different clinical subtypes and prognostic factors (ie, age, gender, bulbar onset, time between onset and diagnosis) in ALS have not been addressed.

Future clinical exercise studies should routinely use random assignment, blinding of investigators, and complete detailed assessments before and after the intervention period. Ideally, participants should be followed up for a minimum of 12 months to reduce within-subject variability and track maintenance of function over time. Controlled experimental studies examining the specific effects of strengthening versus cardiovascular exercise on fatigue in persons with ALS are needed. Future investigations should also compare different exercise modalities and parameters (ie, frequency, load, duration) with nonexercising controls to determine which type of program yields the most benefits with the least risk of disease progression. More studies specifying modifications to exercise programs based on participants' response are also needed to establish guidelines for exercise prescription in this population. Cohort studies separating participants by clinical subtype and prognostic factors may strengthen treatment effects and minimize between-subjects variability by establishing treatment groups that are more homogeneous with respect to disease progression. This separation of participants may also allow future studies to analyze interaction effects between exercise and clinical profiles, making exercise prescription more efficient. Finally, because ALS is a progressive disease with exercise unlikely to yield large changes in disease progression and to maximize statistical power, future investigations should include a trend analyses of pretest/posttest difference scores for exercising and nonexercising groups (eg, Page Test for Linear Trends).

Recommendations to Guide Physical Therapy Practice

This review provides moderately strong evidence in support of moderate-intensity exercise programs for persons with early-stage ALS. In terms of intervention strategies for persons with ALS, the objectives should be to facilitate the healthy innervation of neurons and synaptic networks, to slow the degeneration of neurons, and to maintain cardiopulmonary efficiency, muscle strength, and endurance without overstressing the mechanical, bioelectrical, and metabolic properties of the muscle fibers, particularly, the fast twitch fatigable muscles. Exercise intervention should serve as pivotal area of research for physical therapists, particularly to document the neurophysiological and functional performance changes associated with different exercise programs.

In human studies, there is moderately strong evidence suggesting that participants who were in the early stages of

ALS and exercised had slightly better outcomes with respect to respiratory function, strength, and function compared with early-stage participants who did not exercise. Moderate exercise was not associated with more rapid disease progression. In the animal studies, mice performing moderate exercise on a treadmill or a running wheel most often did not have more rapid disease progression. Unfortunately there was insufficient evidence from these studies to recommend specific exercise guidelines for clinical practice. Integrating the evidence from human and animal research suggests that the type, frequency, intensity, and duration of an exercise program must be matched to each participant and modified according to disease progression and physical ability.

Integrating the evidence presented in this review of ALS with literature on comprehensive rehabilitation programs for persons with other types of neuromotor disease,^{3,54} the following recommendations are applicable when physical therapists are treating individuals with ALS on an outpatient basis:

- Work closely with a multidisciplinary team and be familiar with the disease process of ALS to carefully balance physical performance parameters with disease-related morbidity and drug and respiratory management strategies.
- Use objective measurements such as respiratory function tests (FVC) and strength measurements (manual muscle tests or isometric manual muscle tests using a hand-held dynamometer) to document the clinical picture of the disease process for each patient.
- Couple the clinical picture of the individual with their response to exercise to determine whether strengthening and/or conditioning exercises are appropriate and safe, and when the exercise program should be adjusted to optimize physical function.
- Concentrate exercise interventions in the early stages of the disease when the individuals have sufficient strength, respiratory function, and endurance to exercise without excessive fatigue.
- Carefully evaluate each individual with ALS every few months to gather adequate information to safely adjust strengthening and conditioning exercise.
- Approach exercise programs with caution for individuals with later stage ALS who have low respiratory capacity and/or poor functional scores.
- Use available technology (eg, assistive devices, body weight-supported systems) to optimize exercise regimens according to the individuals' desire to maintain strength, endurance, mobility, and independence without taxing the neuromusculoskeletal system.

CONCLUSIONS

Based on available evidence from human and animal studies, strengthening and cardiovascular exercises may help maintain function and do not adversely affect disease progression in persons with ALS. However, the current evidence is not sufficiently detailed to recommend specific exercise guidelines or outline a specific exercise prescription for persons with ALS. Physical therapists should participate in

randomized clinical trials to better define appropriate exercise interventions for persons with ALS. Based on this evidence-based review, physical therapists working with persons with ALS should base exercise prescription on observed clinical progression of disease, physical ability, interest in participating in an exercise program, and response to exercise.

REFERENCES

1. Simmons Z. Management strategies for patients with amyotrophic lateral sclerosis from diagnosis through death. *Neurologist*. 2005;11:257–270.
2. Cozzolina M, Ferri A, Ciri MT. Amyotrophic lateral sclerosis: From current developments in the laboratory to clinical implications. *Antioxidants Redox Signal*. 2007;10:406–430.
3. McCrate ME, Kaspar BK. Physical activity and neuroprotection in amyotrophic lateral sclerosis. *Neuromolecular Med*. 2008;10:108–117.
4. Jackson CB, Bryan WW. Amyotrophic lateral sclerosis. *Semin Neurol*. 1998;18:27–39.
5. Wicklund MP. Amyotrophic lateral sclerosis: Possible role of environmental influences. *Neurol Clin*. 2005;23:461–484.
6. Francis K, Bach JR, DeLisa JA. Evaluation and rehabilitation of patients with adult motor neuron disease. *Arch Phys Med Rehabil*. 1999;80:951–963.
7. del Aguila MA, Longstreth WT Jr, McGuire V, et al. Prognosis in amyotrophic lateral sclerosis: A population-based study. *Neurology*. 2003;60:813–819.
8. Lomen-Hoerth C. Amyotrophic lateral sclerosis from bench to bedside. *Semin Neurol*. 2008;28:205–211.
9. Miller RG, Rosenberg JA, Gelinas DF, et al. Practice parameter: The care of the patient with amyotrophic lateral sclerosis (an evidence-based review). *Neurology*. 1999;52:1311–1323.
10. Rowland L. Diagnosis of amyotrophic lateral sclerosis. *J Neurol Sci*. 1998;160(suppl):S6–S24.
11. Bromberg MB, Forshew DA. Motor neuron disease. In: Pourmand R, ed. *Neuromuscular Diseases: Expert Clinicians' Views*. Boston, MA: Butterworth Heinemann; 2001:67–103.
12. Mazzeo RS, Cavanagh P, Evans WJ, et al. ACSM position stand: Exercise and physical activity in older adults. *Med Sci Sports Exerc*. 1998;30:992–1008.
13. Strong MJ, Lomen-Hoerth C, Caselli RJ, et al. Cognitive impairment, frontotemporal dementia, and the motor neuron diseases. *Ann Neurol*. 2003;54(suppl 5):S20–S23.
14. Agosta F, Luisa Gorno-Tempini M, Pagani E, et al. Longitudinal assessment of grey matter contraction in amyotrophic lateral sclerosis: A tensor based morphometry study. *Amyotroph Lateral Scler*. 2008;1–4; [Epub ahead of print].
15. Rowland LP, Schneider NA. Medical progress. Amyotrophic lateral sclerosis. *N Engl J Med*. 2001;344:1688–1700.
16. Rothstein J, Van Kammen M, Levey AI, et al. Selective loss of flial glutamate transporter GLT-1 in amyotrophic lateral sclerosis. *Ann Neurol*. 1995;38:73–84.
17. Veldink JH, Kalmijn S, Groeneveld GJ, et al. Physical activity and the association with sporadic ALS. *Neurology*. 2005;64:241–245.
18. Mitsumoto H. Animal models of ALS. In: Mitsumoto H, Chad DA, Pioro EP, ed. *Amyotrophic Lateral Sclerosis*. Philadelphia, PA: FA Davis; 1998:285–302.
19. Sanjak M, Konopacki R, Capasso R, et al. Dissociation between mechanical and myoelectrical manifestation of muscle fatigue in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2004;5:26–32.
20. Caroni PAL, Schneider C. Intrinsic neuronal determinants locally regulate extrasynaptic and synaptic growth at the adult neuromuscular junction. *J Cell Biol*. 1997;136:679–692.
21. Boille SYK, Lobsiger CS, Copeland NG, et al. Onset and progression in inherited ALS determined by motor neurons and microglia. *Science*. 2006;312:1389–1392.
22. Boillee S, Vande VC, Cleveland DW. ALS: A disease of motor neurons and their nonneuronal neighbors. *Neuron*. 2006;52:39–59.
23. Lichtman JW, Sanes J. Watching the neuromuscular junction. *J Neurocytol*. 2003;32:767–775.

24. Finsterer J. Lactate stress testing in sporadic amyotrophic lateral sclerosis. *Int J Neurosci*. 2005;115:583–591.
25. Echaniz-Laguna A, Zoll J, Ribera F, et al. Mitochondrial respiratory chain function in skeletal muscle of ALS patients. *Ann Neurol*. 2002;52:623–627.
26. Echaniz-Laguna AZJ, Ponsot E, N'guessan B, et al. Muscular mitochondrial function in amyotrophic lateral sclerosis is progressively altered as the disease develops: A temporal study in man. *Exp Neurol*. 2006;198:25–30.
27. Sanger T, Delgado M, Gaebler-Spira D, et al. The task force on childhood motor disorders. Classification and definition of disorders causing hypertonia in childhood. *Pediatrics*. 2003;111:89–97.
28. Sanger T, Chen D, Delgado M, et al. Definition and classification of negative motor signs in childhood. *Pediatrics*. 2005;10:2005–2016.
29. Siciliano G, Pastorini E, Pasquali L, et al. Impaired oxidative metabolism in exercising muscle from ALS patients. *J Neurol Sci*. 2001;191(1–2):61–65.
30. Turner MR, Parton MJ, Leigh PN. Clinical trials in ALS: An overview. *Semin Neurol*. 2001;21:167–175.
31. Chio A, Logroscino G, Hardiman O, et al. Prognostic factors in ALS: A critical review. *Amyotroph Lateral Scler*. 2008;1–14; [Epub ahead of print].
32. Brinkmann JR, Andres P, Mendoza M, et al. Guidelines for the use and performance of quantitative outcome measures in ALS clinical trials. *J Neurol Sci*. 1997;147:97–111.
33. Kaufmann P. *High-Dose Coenzyme Q10 Shows No Benefit in ALS*. Chicago, IL: American Academy of Neurology; 2008.
34. Forshe D. A multi-center controlled screening trial of safety and efficacy of lithium carbonate in subjects with ALS. Center FNMR ed. ClinicalTrials.gov; 2008.
35. Fan D. Cistanche total glycosides for amyotrophic lateral sclerosis: A randomized control trial study assessing clinical response. Peking University ed. ClinicalTrials.gov; 2008.
36. Lundbeck H. Memantine for disability in amyotrophic lateral sclerosis (MEDALS). Lisbon University ed. ClinicalTrials.gov; 2008.
37. Liu S. Talampanel for ALS. Teva Pharmaceutical ed. ClinicalTrials.gov; 2008.
38. Miller RG, Rosenberg JA, Gelinas DF, et al. Practice parameter: The care of the patient with amyotrophic lateral sclerosis (an evidence-based review). *Muscle Nerve*. 1999;22:1104–1118.
39. Simmons Z, Bremer BA, Robbins RA, et al. Quality of life in ALS depends on factors other than strength and physical function. *Neurology*. 2000;55:388–392.
40. Ashworth HL, Satkunam LE, Deforge D. Treatment for spasticity in amyotrophic lateral sclerosis/motor neuron disease (Review). *The Cochrane Collaboration*. 2008.
41. Lewis MRS. The role of physical therapy and occupational therapy in the treatment of amyotrophic lateral sclerosis. *NeuroRehabilitation*. 2007;22:451–461.
42. Sinaki M. Physical therapy and rehabilitation techniques for patients with amyotrophic lateral sclerosis. *Adv Exp Med Biol*. 1987;209:239–252.
43. Sinaki M, Mulder DW. Rehabilitation techniques for patients with amyotrophic lateral sclerosis. *Mayo Clin Proc*. 1978;53:173–178.
44. Mitumoto H, Chad DA, Pioro EP. Physical Rehabilitation. In: Mitumoto H, Chad DA, Pioro EP, ed. *Amyotrophic Lateral Sclerosis*. Philadelphia, PA: FA Davis; 1998:360–381.
45. Dal Bello-Haas V, Kloos AD, Mitumoto H. Physical therapy for a patient through six stages of amyotrophic lateral sclerosis. *Phys Ther*. 1998;78:1312–1324.
46. Sanjak M, Reddan W, Brooks BR. Role of muscular exercise in amyotrophic lateral sclerosis. *Neurol Clin*. 1987;5:251–268.
47. Sanjak M, Paulson D, Sufit R, et al. Physiologic and metabolic response to progressive and prolonged exercise in amyotrophic lateral sclerosis. *Neurology*. 1987;37:1217–1220.
48. Longstreth WT, Nelson LM, Koepsell TD, et al. Hypotheses to explain the association between vigorous physical activity and amyotrophic lateral sclerosis. *Med Hypotheses*. 1991;34:144–148.
49. Fowler WM Jr. Role of physical activity and exercise training in neuromuscular diseases. *Am J Phys Med Rehabil*. 2002;81(11 suppl):S187–S195.
50. Kilmer DD. Response to aerobic exercise training in humans with neuromuscular disease. *Am J Phys Med Rehabil*. 2002;81(suppl):S148–S150.
51. Kilmer DD. Response to resistive strengthening exercise training in humans with neuromuscular disease. *Am J Phys Med Rehabil*. 2002;81(11 suppl):S121–126.
52. Vignos PJ. Physical models of rehabilitation in neuromuscular disease. *Muscle Nerve*. 1983;6:323–338.
53. Bohannon RW. Results of resistance exercise on a patient with amyotrophic lateral sclerosis. A case report. *Phys Ther*. 1983;63:965–968.
54. McCartney N, Moroz D, Garner SH, McComas AJ. The effects of strength training in patients with selected neuromuscular disorders. *Med Sci Sport Exerc*. 1988;20:362–368.
55. Sackett D, Straus S, Richardson W, et al. Therapy. In: Sackett D, Straus S, Richardson W, et al, eds. *Evidence-Based Medicine: How to Practice and Teach EBM*. 2nd ed. London: Churchill Livingstone; 2000:105–153.
56. Sackett D, Straus S, Richardson W, et al. Prognosis. In: Sackett D, Straus S, Richardson W, et al, eds. *Evidence-Based Medicine: How to Practice and Teach EBM*. 2nd ed. London: Churchill Livingstone; 2000:95–103.
57. Neeper S, Gomez-Panilla F, Choi J, et al. Exercise and brain neurotrophins. *Nature* 1995;373:109.
58. Trejo J, Carro E, Torres-Aleman I. Circulating insulin-like growth factor 1 mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *J Neurosci*. 2001;21:1628–1634.
59. Cohen A, Tillerson JL, Smith AD, et al. Neuroprotective effects of prior limb use in 6 hydroxydopamine treated rats: Possible role of GDNF. *J Neurochem*. 2003;85:299–305.
60. Swain R, Harris AB, Wiener EC, et al. Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. *Neuroscience*. 2003;117:1037–1046.
61. Fordyce D, Farrar RP. Physical activity effects on hippocampal and parietal cortical cholinergic function and spatial learning in F344 rats. *Behav Brain Res*. 1991;43:115–123.
62. Jokić N, Gonzalez de Aguilar JL, Dimou L, et al. The neurite outgrowth inhibitor Nogo-A promotes denervation in an amyotrophic lateral sclerosis model. *EMBO Rep*. 2006;7:1162–1167.
63. Ottawa Panel evidence-based clinical practice guidelines for therapeutic exercises in the management of rheumatoid arthritis in adults. *Phys Ther*. 2004;84:934–972.
64. Beninato M, Gill-Body KM, Salles S, et al. Determination of the minimal clinically important difference in the FIM instrument in patients with stroke. *Arch Phys Med Rehabil*. 2006;87:32–39.
65. Jewell D. *Guide to Evidence Based Physical Therapy Practice*. 1st ed. Boston, MA: Jones and Bartlett Publishers; 2008.
66. Dal Bello-Haas V, Florence JM, Krivickas LS. Therapeutic exercise for people with amyotrophic lateral sclerosis/motor neuron disease (Protocol). *The Cochrane Database of Systematic Reviews*. 2005(2):1–7.
67. Aksu SK, Ayse Y, Yavuz T, et al. The effects of exercise therapy in amyotrophic lateral sclerosis. *Fizyoterapi Rehabilitasyon*. 2002;13:105–112.
68. Pinto AC, Alves M, Nogueira A, et al. Can amyotrophic lateral sclerosis patients with respiratory insufficiency exercise? *J Neurol Sci*. 1999;169:69–75.
69. Drory VE, Goltsman E, Reznik, JG, et al. The value of muscle exercise in patients with amyotrophic lateral sclerosis. *J Neurol Sci*. 2001;191:133–137.
70. Dal Bello-Haas V, Florence JM, Kloos AD, Scheirbecker J, et al. A randomized controlled trial of resistance exercises in individuals with ALS. *Neurology*. 2007;68:2003–2007.
71. Veldink JH, Bar PR, Joosten EA, et al. Sexual differences in onset of disease and response to exercise in a transgenic model of ALS. *Neuromuscul Disord*. 2003;13:737–743.
72. Kaspar BK, Frost LM, Christian L, Umapathi P, et al. Synergy of insulin-like growth factor-1 and exercise in amyotrophic lateral sclerosis. *Ann Neurol*. 2005;57:649–655.
73. Liebetanz D, Hagemann K, von Lewinski F, et al. Extensive exercise is not harmful in amyotrophic lateral sclerosis. *Eur J Neurosci*. 2004;20:3115–3120.
74. Mahoney DJ, Rodriguez C, Devries M, et al. Effects of high-intensity endurance exercise training in the G93A mouse model of amyotrophic lateral sclerosis. *Muscle Nerve*. 2004;29:656–662.
75. Kirkinezos IG, Hernandez D, Bradley WG, et al. Regular exercise is

- beneficial to a mouse model of amyotrophic lateral sclerosis. *Ann Neurol.* 2003;53:804–807.
76. Mitsumoto H, Chad DA, Pioro EP. Treatment Trials. In: Mitsumoto H, Chad DA, Pioro EP, ed. *Amyotrophic Lateral Sclerosis*. Philadelphia, PA: FA Davis; 1998:329–359.
 77. Krivickas L. Pulmonary function and respiratory failure. In: Mitsumoto H, Chad DA, Pioro EP, ed. *Amyotrophic Lateral Sclerosis*. Philadelphia, PA: FA Davis; 1998:382–404.
 78. Dal Bello-Haas V, Florence JM, Krivickas LS. Therapeutic exercise for people with amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev.* 2008(3):1–24.
 79. Armon C. A randomized controlled trial of resistance exercise in individuals with ALS [correspondence]. *Neurology.* 2008;71:864–866.
 80. Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, Caliendo J, Hentati A, Kwon YW, Deng HX, et al. 1994. Motor neuron degeneration in mice that express a human Cu, Zn superoxide dismutase mutation. *Science* 1994;264:1772–5.
 81. Goulart J, Milani PO, Matheus JPC, et al. Biomechanical effects of immobilization and rehabilitation on the skeletal muscle of trained and sedentary rats. *Ann Biomedical Eng* 2008;36:1641–1648.
 82. King A, Rejeski J, Buchner D. Physical activity interventions targeting older adults: A critical review and recommendations. *Am J Prev Med.* 1998;15:316–333.
 83. Li J, Ding YH, Rafols JA, et al. Increased astrocyte proliferation in rats after running exercise. *Neuroscience Lett.* 2005;386:160–164.
 84. Ding Y, Luan XD, Li J. Exercise-induced overexpression of angiogenic factors and reduction of ischemia/reperfusion injury in stroke. *Curr Neurovasc Res* 2004;1:411–420.
 85. Kleim J, Jones TA, Scallert T. Exercise induces angiogenesis but does not alter movement representation within rat motor cortex. *Brain Res.* 2003;934:1–6.
 86. Cotman CW, Berchtold NC. Exercise. A behavioral intervention to enhance brain health and plasticity. *Trends Neurosci.* 2002;25:295–301.
 87. Gardiner P, Dai, Y, Heckman, et al. Ultrastructure of blood-brain barrier and blood-spinal cord barrier in SOD1 mice modeling ALS. *Brain Res.* 2006;1157:126–137.
 88. Barber S, Mead RJ, Shaw PJ. Oxidative stress in ALS: A mechanism of neurodegeneration and a therapeutic target. *Biochim Biophys Acta.* 2006; 1762:1051–1067.
 89. Garbuzova-Davis S, Haller E, Saporta E, et al. Ultrastructure of blood-brain barrier and blood-spinal cord barrier in SOD1 mice modeling ALS. *Brain Res.* 2007;1157:126–137.
 90. Lenman JR. A clinical and experimental study of the effects of exercise on motor weakness in neurological disease. *J Neurol Neurosurg Psychiatry.* 1959;22:182–94.