Study/Type	Quality Rating	Sample Description	Method	Outcomes	Key Findings
Review of Exercise evidence 2015-2018					
Plowman, EK.;Tabor-Gray, L; Rosado, M; Vasilopoulos, T; Robison, R; Chapin, JL.; Gaziano, J; Vu, T; Gooch, Impact of expiratory strength training in amyotrophic lateral sclerosis: Results of a randomized, sham-controlled trial. Muscle & nerve 2018 RCT – double blinded	Class I	N = 48 patients with ALS (29 men) ALSFRS-R >30 FVC > 65%	Compared outcomes of an 8-week expiratory strength training program to control 'sham' group; program of 5 days a week of 5x5 reps	Primary outcome – MEP Secondary outcomes – Cough function Swallow function FVC ALSFRS-R	46 patients completed; treatment group had significantly higher increase in MEP; although not significant, treatment group maintained Peak cough flow
Merico, A; Cavinato, M; Gregorio, C; Lacatena, A; Gioia, E; Piccione, F; Angelini, C Effects of combined endurance and resistance training in Amyotrophic Lateral Sclerosis: A pilot, randomized, controlled study. European Journal of Translational Myology 2018 RCT – blinded, pilot	Class II	N= 46 enrolled Mild-mod disease ALSFRS-R≥34 ambulatory	Compared randomly allocated patients in two groups; moderate aerobic with isometric exercise compared to 'standard neuromotor rehabilitation'; daily exercise for 5 weeks	Muscle strength Fatigue Cardiovascular parameters; VO2submax FIM 6min walk test	8 dropped out with 38 analyzed Improvement in FIM for both groups. Muscle power, VO2submax and fatigue improved in exercise group; patient baseline was rate of progression 0.4 pts/month on ALSFRS-R
Braga, Anna; Caroline Marques; Pinto, Anabela; Pinto, Susana; de Carvalho, Mamede. Neurology Research International 2018 The Role of Moderate Aerobic Exercise as Determined by Cardiopulmonary Exercise Testing in ALS RCT – single blind, quasi-randomized (based on geography)	Class II	N = 48 patients with ALS (32 male) Onset 6-24 months ambulatory ALSFRS ≥ 30 FVC ≥ 70%	Quasi-randomized study comparing group with supervised program and twice weekly treadmill exercise with defined moderate exercise intensity as determined by cardiopulmonary exercise testing (CPET), with group receiving 'standard' of care (home exercise	ALSFRS-R FVC Nocturnal pulse oximetry VO2	Monitored aerobic exercise as defined by CPET can be done in patients with ALS and was associated with improved outcome (less decline) as demonstrated by ALSFRS-R, over a 6-month period. Standard group had fewer participants complete the CPET

			program – this was not well described)		
Clawson, Lora L; Cudkowicz, Merit; Krivickas, Lisa; Brooks, Benjamin R; Sanjak, Mohammed; Allred, Peggy; Atassi, Nazem; Swartz, Amy; Steinhorn, Gabrielle; Uchil, Alpa; Riley, Kristen M; Yu, Hong; Schoenfeld, David A; Maragakis, Nicholas J; NEALS Consortium A randomized controlled trial of resistance and endurance exercise in amyotrophic lateral sclerosis. Amyotrophic Lateral sclerosis & Frontotemporal Degeneration 2018 RCT unblinded	Class II	N = 59 patients with ALS	6-month parallel; randomly assigned to one of three groups; all exercises performed 3x weekly for 6 months	Primary evaluated compliance and tolerability with 3 different exercise regimes: resistance, endurance and passive stretching/range of motion (SROM) (control) in home-based program Outcomes also included ALSFRS-R, FVC, Fatigue Severity Scale, strength measures, ALSSQoL-R, Ashworths Scale, VO2max	75% completed the study; all three groups met predetermined threshold for tolerance, with SROM better tolerated than endurance exercise No evidence of harm was identified; no improvements in outcomes noted but study was not powered to evaluate efficacy
Lunetta,C; Lizio, A; Sansone, VA; Cellotto, NM; Maestri, E; Bettinelli, M; Gatti,V; Melazzini, MG; Meola, G; Corbo, M. Strictly monitored exercise programs reduce motor deterioration in ALS: preliminary results of a randomized controlled trial. Journal of neurology 2016 RCT – single blinded	Class II	N = 60 patients with ALS (38 men) Onset ≤ 24 months FVC ≥ 70% Min-mod disease severity	Evaluated the effects of three strictly monitored exercise programs (SMEP) compared to "usual care (UCP)" SMEP – active exercise plus cycloergometer, or active exercise alone, or passive exercises.	ALS Functional Rating Scale (ALSFRS-R), % Forced Vital Capacity (FVC %), and McGill Quality of Life (MGQoL) questionnaire	T180 and T360, SMEPs group had significantly higher ALSFRS-R score compared to the UCP group; no differences in other measures on survival, respiratory decline and MGQol were found (SMEP group 21 men, 9 women)
Kitano, K; Asakawa,T; Kamide,N; Yorimoto,K; Yoneda,M; Kikuchi, Y; Sawada,M; Komori,T.	Class III	N = 21 patients with ALS ALSFRS-R ≥30	Unsupervised structured home exercise group (N=21) compared to historical control of N	ALSFRS-R Manual muscle testing; peak cough flow	N=15 completed study; ALSFRS-R was maintained in Home exercise group; home

Effectiveness of Home-Based Exercises Without Supervision by Physical Therapists for Patients With Early-Stage Amyotrophic Lateral Sclerosis: A Pilot Study. Archives of Physical Medicine & Rehabilitation 2018 Prospective cohort			= 84 in a 6-month supervised exercise program; Home group did stretching, strengthening and functional activities.		exercise without supervision was safe and feasible
Plowman,EK; Watts,SA; Tabor,L; Robison,R; Gaziano,J; Domer,AS; Richter,J; Vu,T; Gooch,C Impact of expiratory strength training in amyotrophic lateral sclerosis. Muscle & nerve 2016 Case Series	Class III	N = 25 patients with ALS Reduced MEP FVC > 60%	Open study lead in evaluation of a 8 week expiratory muscle training program of 5 days a week of 5x5reps	MEP Swallow function Cough spirometry	19 entered active treatment, final analysis on 15 patients with significant increase in MEP from baseline
Kato,N; Hashida,G; Kobayashi,M; Konaka,K Physical therapy improves lower limb muscle strength but not function in individuals with amyotrophic lateral sclerosis: A case series study. Annals of Physical & Rehabilitation Medicine 2018 Case series	Class IV	N = 10 patients (9 men) with ALS able to walk 10m without aid	2-3 weeks of physical therapy 5 days/wk of strengthening and other exercises	ALSFRS-R subscores Knee extension muscle strength	Knee strength improved at end of physical therapy.
Jensen, L; Djurtoft, JB; Bech, RD; Nielsen, JL; Jorgensen, LH; Schroder,HD; Frandsen,U; Aagaard, P; Hvid, LG. Influence of Resistance Training on Neuromuscular Function and Physical Capacity in ALS Patients.	Class IV	N = 6, ambulatory without assistance at study onset	Exploratory open-label, repeated measure trial with 12-week lead in as control/benchmark to explore effect of resistance training on functional outcomes;	(ALSFRS-R, TUG, 30s chair rise), voluntary muscle activation, strength (four muscle groups), neuromuscular function, histology	5 completed; No lessening of ALSFRS-R was found

Journal of Neurodegenerative Diseases Print 2017 Case series			12 weeks intervention; exercises targeted upper body, lower limbs and trunk, were supervised and performed in small groups 2-3x/week, with adjustments to exercises made individually; participants were given protein supplement after each session		
Braga, Anna; Pinto, Anabela; Pinto, Susana; de Carvalho, Mamede. European journal of physical & rehabilitation medicine 2018 Tele-monitoring of a home-based exercise program in amyotrophic lateral sclerosis: a feasibility study Case series	Class IV	N = 10 patients with ALS onset 6-24 months ALSFRS-R≥30 FVC > 70%	Assessment of a tele-monitoring system (TMS) for home exercise program	Compliance as captured by the TMS	Telemonitoring over 6 months was feasible and safe for monitoring a home aerobic (15 min of under 75% max HR) exercise program
Review of Exercise evidence 1998-2015					
Cheah et al., Amyotrophic Lateral Sclerosis 2009 INSPIRATIonAL – INSPIRAtory muscle training in amyotrophic lateral sclerosis RCT – double blind	Class I	N = 19 non ventilator dependent	12 week inspiratory muscle training program with 10 min 3x/d with IMT vs sham exercise	FVC, MEP, SNIP, MIP,VC; evaluated during and 8 weeks post	18 completed study. FVC, MEP, SNIP, MIP, VC improved both groups; non-sig trend to improved MIP in treatment group; partially reversed with treatment cessation
Dal Bello-Haas, V et al. Neurology 2007	Class II	N = 27 with ALS FVC ≥ 90% ALSFRS ≥ 30	Resistance exercise group (home program of resistance exercise 3x/wk and daily	ALSFRS and SF-36 QOL physical function subscore	18 completed the study (8 exercise); resistance exercise group had

A randomized controlled trial of resistance exercise in individuals with ALS RCT single blind			stretching vs regular care (daily stretching) x 6 months; exercise was moderate load, moderate intensity	Fatigue Severity Score; FVC and maximum voluntary isometric contraction	significantly better function, as measured by total ALS Functional Rating Scale and upper and lower extremity subscale scores, and quality of life without adverse effects as compared with subjects receiving usual care; no change on fatigue
Drory, et al. Journal of the Neurological Sciences, 2001 The value of muscle exercise in patients with amyotrophic lateral sclerosis RCT - unblinded	Class II	N = 25 (14 male) Able to walk Not on any ventilation support	treatment group received personalized sub max effort strength program for trunk and limbs, performed twice daily 15 min; control was regular daily activity; evaluated x 1 year	ALSFRS-R Ashworth scale Fatigue severity scale VAS for pain SF-36 Manual muscle strength testing	At 3 months (N=18) patients who performed regular exercise showed less deterioration on ALSFRS and Ashworth scales, but not on other parameters. At 6 months, there was no significant difference between groups, although a trend towards less deterioration in the treated group on most scales was observed. At 9 and 12 months, there were too few patients in each group for statistical evaluation Moderate regular physical activity has mild positive effect in short term on motor

					deficit, disability, fatigue and HRQOL
Pinto, S; Swash, M and de Carvalho, M. Amyotrophic Lateral Sclerosis 2012 Respiratory exercise in amyotrophic lateral sclerosis RCT	Class II	N = 26 ALS patients (18 male) Disease < 24 months ALSFRS > 24/40 FVC ≥ 70%	Patients performed an 8-month respiratory muscle strengthening programme using the ‘‘Threshold IMT’’. They were randomized in 2 groups: the efficient load group (G1) and non-efficient load group (G2). However, patients in G2 also performed the exercise with efficient load in the	ALSFRS Secondary: respiratory measures, physiological measures, quality of life	N = 20 completed 8 months. Within-group analysis suggested that inspiratory exercise promotes a transient improvement in the respiratory subscore and in the maximal voluntary ventilation, peak expiratory flow, and sniff inspiratory pressure. Trial went to open extension - see Pinto 2013

			last four months (delayed start study design).		
Kamide, N et al. Neurology and Clinical Neurosciences 2014 Identification of the type of exercise therapy that affects functioning in patients with early-stage amyotrophic lateral sclerosis: a multicenter, collaborative study Retrospective Cohort	Class III	N = 156 ALSFRS-R ≥ 30 Not ventilated Followed for exercise for at least 4 months	To investigate the types of exercise therapy performed correlation with functioning in early-stage amyotrophic lateral sclerosis patients, analyzed over 6 months.	ALSFRS-R	The combination of performance task training (walking, standing and ADL tasks) appears to alleviate functional decline in early-stage amyotrophic lateral sclerosis patients.
Aksu, S and Citak-Karakaya, I. The Pain Clinic, 2002 Effect of exercise therapy on pain complaints in patients with amyotrophic lateral sclerosis Case cohort	Class III	N = 26 patients with ALS and reports of pain Able to walk 5m	Comparison of pain outcomes of a home vs supervised exercise program; exercise program was 8 weeks of 3 consecutive days, 45-60 min with stretching, proprioception, and mobility training, followed by home program. Home program was active/active-assist ROM and stretching, 10 reps 3x/d. Convenience sample based on distance	Visual analog scale, isometric muscle strength	Equal male and female in each group. Supervised exercise had improved pain and strength at 8 weeks
Pinto, S and de Carvalho, M. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2013 Can inspiratory muscle training increase survival in early-	Class IV	N = 18 compared to N=16 historical matched controls	Longitudinal followup of patients performing inspiratory muscle exercise	FVC Survival Patients in survived signifi cantly longer than patients in G2 (36.99 13.1 months vs. 24.06	Patients in exercise group survived significantly longer than patients in control

affected amyotrophic lateral sclerosis patients? Cohort				11 months, respectively, p 0.001).Signifi cant prognostic variables in univariate Kaplan-Meier analysis were IMT and FVC for the total population. FVC was also a sig nifi cant prognostic factor for G1 and diagnostic delay was a signifi cant prognostic factor for G2	
Sanjak, M et al. Arch Phys Med Rehabil 2010 Supported treadmill ambulation for amyotrophic lateral sclerosis: a pilot study Case Series	Class IV	N = 9 ALS patients ambulatory	Repetitive rhythmic exercise-supported treadmill ambulation training (30min total; 5min of exercise with 5min of rest) performed 3 times a week for 8 weeks.	ALSFRS-R VC Manual muscle test Rate of perceived exertion Fatigue Severity Scale Gait performance	6/9 completed the study. Improvements in gait parameters (speed, distance, stride) improved after 4 weeks and maintained after 8 weeks; less fatigue and RPE
Nardin, R et al J Clin Neuromuscular Disease 2008 Diaphragm training in amyotrophic lateral sclerosis Case series - pilot	Class IV	N = 8 FVC 50-80%	Subjects diaphragm training, a method of breath control designed to improve respiratory muscle strength and efficiency; patients evaluated at 6 and 12 weeks.	FVC Respiratory measures Quality of life measures	There was no significant improvement in any outcome measure after instituting diaphragm training. There was a nonsignificant trend toward a slower rate of decline in respiratory function in those subjects who mastered the technique;

					however, only half the subjects were able to successfully change their pattern of breathing.
Eidenberger, M and Nowotny, S. Neurorehabilitation 2014 Inspiratory muscle training in patients with amyotrophic lasteral sclerosis: a systematic review Systematic Review		N = 73 pooled	Review the current literature to assess the efficacy of inspiratory muscle training for ALS		4 studies provided limited evidence for IMT
Dal Bello-Haas, V and Florence, JM. Cochrane Collaboration 2013 Therapeutic exercise for people with amyotrophic lateral sclerosis or motor neuron disease Systematic Review		2 studies combine for N = 43 participants	Randomized and quasi-randomized studies of exercise in ALS	ALSFRS, quality of life, fatigue, strength at 3 months	After three months, when the results of the two trials were combined there was a significant mean improvement in the ALSFRS measure of function in favour of the exercise groups (mean difference 3.21, 95% confidence interval 0.46 to 5.96). No statistically significant differences in quality of life, fatigue or strength
Ashworth NL, Satkunam LE, Deforge D Cochrane Collaboration 2012 Treatment for spasticity in amyotrophic lateral sclerosis/motor neuron disease		1 study with N=25	Cochrane review of all randomized or quasi-randomized trials of any treatment intervention for spasticity in amyotrophic lateral sclerosis	Reduction in spasticity at 3 months or greater as measured by MAS; secondary outcomes included any validated physical, physiological,	Only 1 article identified; See Drory 2001

Systematic Review			to determine impact of interventions on spasticity; update of previous reviews 2005 and 2008	quality of life, adverse events	
Lui, AJ and Byl, NN JNPT 2009 A systematic review of the effect of moderate intensity exercise on function and disease progression in amyotrophic lateral sclerosis Systematic Review		N = 87 pooled for strength and ALSFRS	Systematic review of moderate exercise (human and animal); at least 6 months followup	Functional scores, strength, respiratory function, disease progression	4 small clinical and 1 systematic review supporting benefit of moderate exercise in early ALS, without evidence of harm