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CLINICAL TRIAL

A randomized controlled trial of resistance and endurance exercise in amyotrophic lateral sclerosis

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Abstract

Objective: Evaluate the safety and tolerability of resistance and endurance exercise in ALS participants as measured by their ability to complete this six-month study. *Methods:* Participants were randomized to Resistance, Endurance, or Stretching/Range of Motion (SROM the exercise regimen prescribed for most ALS patients) exercises. All exercises were performed at home with an individualized regimen designed by a physical therapist trained in ALS management. Primary outcome measures were tolerability of the exercises at 24 weeks defined by 50% of participants completing at least 50% of the prescribed exercise regimen. Secondary outcome measures included the ALSFRS-R, pulmonary FVC, and other measures of ALS function. *Results:* At 12 and 24 weeks, all three exercise regimens were tolerated according to our pre-specified criteria. Compliance to the prescribed exercise regimen was the highest in the resistance and SROM arms of the study. All three forms of exercise were considered safe as there were no differences in the rates of disease progression among groups. There were no differences in the secondary outcome measures and feasibility for evaluating these measures was successful. In a post-hoc analysis, there was a trend towards fewer falls in the Resistance and Endurance groups. *Conclusions:* This study demonstrates that SROM, resistance, and endurance exercise are all safe to be performed with the specified regimen without any worsening of outcomes as related to ALS function. All three forms of exercise were tolerated with resistance and SROM exercises showing the highest compliance over the 24 week-period.

KEYWORDS: *ALS*; *tolerability*; *benefit*; *motor neuron disease*; *clinical trial*

Introduction

Some of the first questions asked by patients with a new diagnosis of ALS include: "Does exercise help slow the progression of the disease?", "Is there any harm in exercising?", or "What type of exercise is most appropriate for ALS patients?" However, there is a paucity of answers for people who suffer from an illness that affects their strength above all else.

A randomized, controlled, large study evaluating the potential benefits of resistance and endurance exercise in ALS has not been systematically undertaken. In the American Academy of Neurology Practice Parameter for ALS, no recommendations were made regarding specific types of physical exercise in ALS management (1). Therefore, there is no consensus on the possible benefits, or hazards, of exercise formulated for ALS.

In healthy individuals, an exercise program based on resistance exercise results in an increase in muscle strength and power. This increase in strength results in more effective recruitment of motor units and an increase in the cross-sectional area of the muscle (2–4). Those exercises which are based on endurance result in an increase in the

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oxidative potential of skeletal muscle (5) and lead to an increase in mitochondrial volume (6), improvements in exercise capacity, reduction in psychological stress, reductions in diseases including heart disease, diabetes, and cancer (7). Stretching exercises increase tendon flexibility. The benefits include the improvement of joint range of motion and function (8) and the enhancement of muscular performance (9,10).

Some epidemiologic data have shown a higher incidence of ALS in patients performing intense physical activity at work or for leisure before onset of the disease (11), although this has been debated (12,13). Others have noted a shared mechanism underlying a favorable cardiovascular fitness profile and ALS susceptibility (14). While some studies have found that the relationship between physical activity and ALS is inconclusive in the general population, there may be higher numbers of cases of ALS in professional soccer and American football players (15). The differences in some of these epidemiologic studies may lead clinicians to caution their patients to avoid regular exercise in ALS after a diagnosis. However, a lack of physical activity also results in deconditioning which may compound weakness induced by ALS itself. If such inactivity occurs, contractures accompanied by joint tightness may result in pain and a reduced capacity to carry out activities of daily living (16).

The scientific basis for many, if not most, studies in ALS has relied on the study of molecular pathways and therapeutics in the transgenic mutant SOD1 mouse (mSOD1). Several studies in these mice have suggested potential benefits from exercise including motor neuron protection, delaying disease onset and improving survival (17–20). In patients with ALS, numerous small studies and case reports have also highlighted potential roles for various forms of exercise in ALS (5,21–26).

In light of these observations, individuals with ALS were asked to participate in a randomized, six month, parallel group study which included exercise in one of three types: weightlifting (resistance exercise), stationary bicycling (endurance exercise), and stretching/range of motion exercise (SROM) (the exercise regimen prescribed for most ALS patients).

Methods

A six-month, parallel-group, randomized study of adults classified as having possible, laboratory supported probable, probable, or definite ALS according to the El Escorial criteria was conducted (clinical trials identifier #NCT01521728). The study protocol was approved by the institutional review boards of the participating institutions and all participants provided written informed consent. A detailed description of the study procedures is found in Supplemental tables.

Sample size

The sample size of 20 patients for each of the three arms of the trial was based on safety, tolerability, and feasibility, rather than statistical considerations for efficacy. We considered an exercise program tolerable if 10 or more participants within each group were able to meet the primary outcome measures. With 20 participants per group we would have over an 89% chance of declaring a program tolerable if the true rate of tolerability was over 70%. We would have an 87% chance of declaring a program intolerable if the true rate of tolerability was less than 45%. The power calculation was made on a binomial distribution similar to that which can be performed by accessing http://stattrek.com/online-calculator/binomial.aspx.

Primary outcomes

All enrolled participants were considered evaluable for tolerability. In the tolerability analyses, a participant was regarded as a treatment success if the participant completed week 24 of the study while being compliant with $\geq$50% of the scheduled exercise days. For the resistance exercise arm of the study, the participant was compliant with a single 'exercise day' if the participant completed $\geq$50% of the total number of repetitions assigned. For the endurance exercise arm of the study, the participant was compliant with a single 'exercise day' if the participant completed $\geq$50% of the total time assigned at the target heart rate or Borg scale (27). For the stretching and range of motion arm of the study, the participant was compliant with a single 'exercise day' if the participant completed $\geq$50% of the number of repetitions for each muscle group.

Compliance was calculated at each study visit by study coordinators and was based on criteria for both compliance of the regimen within each 'exercise day' as well as compliance of >50% of the total number of exercise days during the period of observation. These broad compliance measures were chosen a priori, recognizing that as disease progressed the capacity to complete all the exercises required within a session could be limited. These broad criteria allowed us to ensure that participants would have at least some consistent measures of exercise intensity and frequency weekly.

Study design

Participants meeting the eligibility criteria and accepted into the study were randomized in a 1:1:1 ratio to the three study arms, stratified by site. The Biostatistics Center at Massachusetts General Hospital (MGH) generated the site-specific randomization schedules using permuted blocks of

size 3. The randomization schedules were implemented within the study Electronic Data Capture (EDC) system by the Data Coordination Center at MGH NCRI (Neurological Clinical Research Institute). Due to the nature of the study design, the participants, site staff, and all other study staff including project and data management personnel were unblinded to the exercise assignment once the randomization process was completed in the EDC system.

To improve study participant retention, we incorporated a relatively simple exercise regimen and combined this with our attention to instruction as to how to perform the exercises safely. We elected a home-based exercise program rather than one requiring travel to and from the medical center to perform each exercise session.

To ensure reproducibility in each arm of the trial, the participant and 'exercise partner' were initially trained by a physical therapist to perform the prescribed exercises. Proper technique was reviewed at each subsequent participant visit by the physical therapist. The participants were not blinded to the form of exercise. However, to reduce bias from the study, a 'clinical evaluator' was blinded to the treatment and collected all the data for the secondary outcome measures.

Resistance exercise

Resistance was administered concentrically using a series of adjustable cuff weights for the upper limbs and hip flexion. Knee flexion and extension were administered with a weight bench using a leg exercise attachment and free weights. The cuff weights and weight bench were used at home. In order to adjust for a participant's evolving capacity to lift a prescribed amount of weight, a participant's 1 repetition maximum (1RM) was used to determine the weight they were assigned for each week as detailed in Supplemental Table 1.

Endurance exercise

The minicycle was used for this arm of the trial. It can be used from a sitting position (chair or wheelchair) for lower limb exercise and then placed on a tabletop for upper limb use. This afforded an element of safety since the seated position reduced difficulties with balance and potential falls. In order to adjust for a participant's capacity for exercise over time, the endurance exercise was adjusted to the targeted heart rate. The endurance exercise included cycling, involving both the lower and upper limbs. The specific regimen is detailed in Supplemental Table 2.

Stretching and range of motion exercise

Stretches were done passively, with the help of a partner. Actions included stretching of the following: deltoids, triceps, hand/wrist flexors, gastrocnemius, hamstring, and quadriceps (Supplemental Table 3).

Outcome measures

The following outcome measures were performed at the baseline visit: (1) The ALSFRS-R (ALS Functional Rating Scale-Revised) – a widely used and validated functional scale. ALSFRS-R scores correlate with change in strength over time and are closely associated with quality of life measures and predicted survival (1); (2) Pulmonary Forced Vital Capacity (FVC), Quantitative Strength Measurement using Hand Held Dynamometry, and Grip Strength using the Jaymar grip dynamometer; (3) The ALSSQoL-R was designed specifically to assess the quality of life for ALS patients (28); (4) The Fatigue Severity Scale consists of nine statements assessing the impact of fatigue on daily function (29); (5) The Ashworth Spasticity Scale is a standard measure for spasticity and has been used in a previous ALS clinical trial (21); (6) The maximum oxygen consumption (VO_2 max) was used as one standard measure of endurance exercise. A visual analogue scale (VAS) for fasciculations, spasticity and muscle cramping/pain was employed.

Following the baseline visit, research participants returned for in-person visits at 2, 4, 12, 20 and 24 weeks following the baseline visit. Participants received a phone call from the coordinator to assess adverse events and compliance with the exercise regimen at weeks 6, 10, 14,18, and 22 weeks after the baseline visit.

Results

Recruitment and demographics

Recruitment began in April 2012 and the last participant enrolled in September 2015. Participantswere randomized into one of three groups: Stretching and Range of Motion, resistance exercise, and endurance exercise (Figure 1). Sixty-five patients were screened at four sites. Baseline characteristics of the enrolled participants are shown in Table 1. We recorded baseline characteristics for ALS participants for a number of demographic measures including age and gender. Baseline measures for our outcome measures including ALSFRS-R and pulmonary forced vital capacity were also measured. As riluzole is approved for use in ALS, the percentage of participants taking this medication was also recorded.

Safety

There were four serious adverse events in this study. Two were in the resistance exercise group and neither was thought to be related to the prescribed exercise. The first one was a female who had a

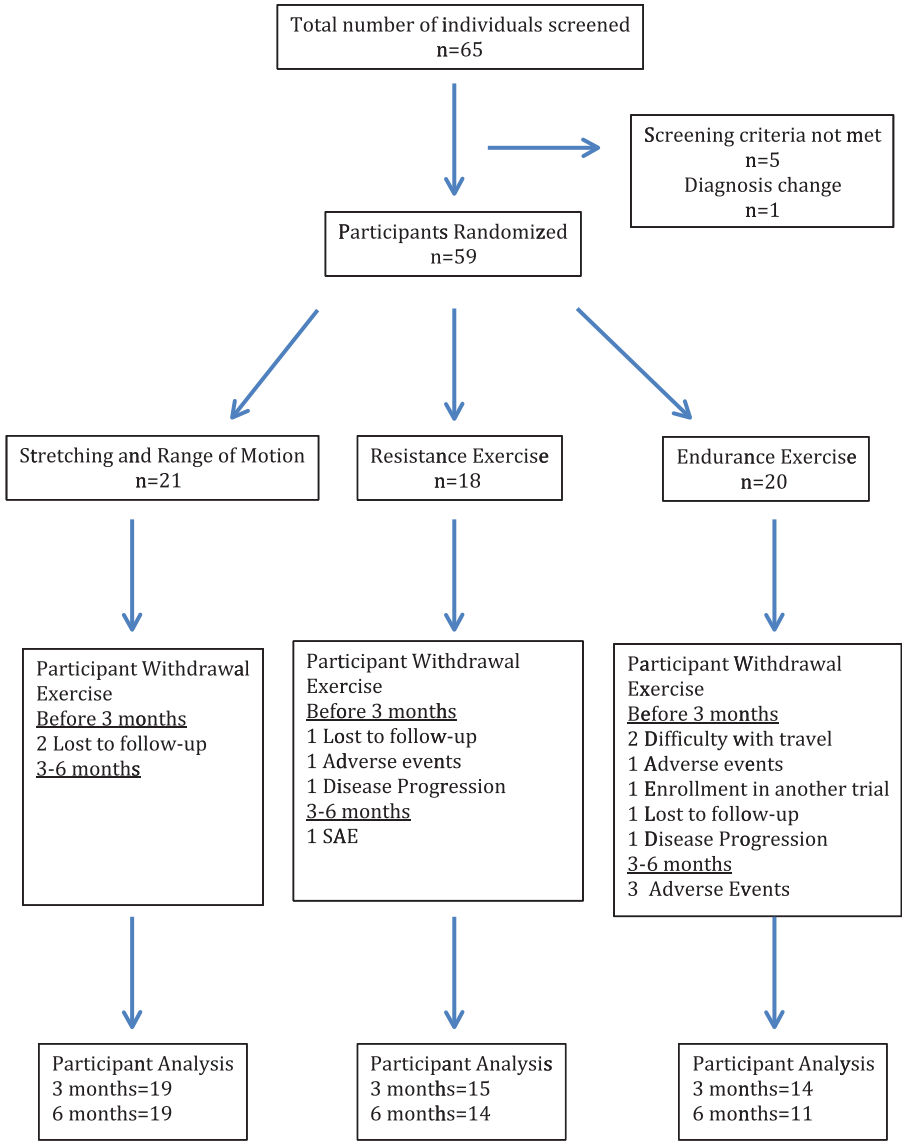

Figure 1. Trial enrollment, randomization, and withdrawals during the six month study.

Table 1. Participant demographic and clinical features.

		Randomization Groups		
	ALL $n=59$	Stretching $n=21$	Resistance $n=18$	Endurance $n=20$
Mean age in years (SD)	59.55 (10.91)	57.68 (9.72)	63.65 (10.55)	57.82 (11.88)
Males (%)	39 (66.1%)	15 (71.4%)	9 (50.0%)	15 (75.0%)
Mean time from diagnosis to baseline in months (SD)	8.63 (9.69)	11.08 (13.21)	7.25 (7.21)	7.30 (6.80)
Bulbar onset (%)	14 (23.7%)	4 (19.0%)	6 (33.3%)	4 (20.0%)
Number of subjects with familial ALS (% of total)	1 (1.7%)	0 (0%)	0 (0%)	1 (5.0%)
Mean ALSFRS-R at baseline (SD)	39.47 (4.47)	39.67 (3.71)	39.17 (4.91)	39.55 (4.97)
Mean predicted vital capacity at baseline (SD)	92.78 (18.18)	101.19 (17.9)	88.33 (19.05)	87.95 (15.02)
Concomitant riluzole (%)	52 (88.1%)	18 (85.7%)	17 (94.4%)	17 (85.0%)

pulmonary embolism thought to be related to the prescription of oral contraception medications a few days prior to the event. The second was the discovery of a lung neoplasm in a participant. A third participant in the endurance exercise group had two serious adverse events: pneumonia and respiratory distress. There were no deaths in any of the three arms during the 24-week period of the study (Table 2). The most common adverse events were primarily musculoskeletal and injury related.

Table 2. Serious adverse events.

		Stretching			Resistance			Endurance			Total		
SOC Abbreviation	Preferred Term	N	E	%	N	E	%	N	E	%	N	E	%
Neoplasms	Lung Neoplasm	0	0	0	1	1	5.6	0	0	0.0	1	1	1.7
Respiratory	Pneumonia Aspiration	0	0	0	0	0	0.0	1	1	4.8	1	1	1.7
	Pulmonary Embolism	0	0	0	1	1	5.6	0	0	0.0	1	1	1.7
	Respiratory Distress	0	0	0	0	0	0	1	1	5.0	1	1	1.7
Total	Total	0	0	0	2	2	11.1	1	2	5.0	3	4	5.1

N = Number of Participants.
E = Number of Events.
% = Number of subjects with an Event/Number of subjects × 100.

Table 3. Most frequent adverse events.

	Stretching			Resistance			Endurance			Total		
Adverse Event	N	E	%	N	E	%	N	E	%	N	E	%
Fall	13	20	61.9	5	8	27.8	7	12	35	25	40	42.4
Muscle Spasms	5	22	23.8	3	5	16.7	3	3	15.0	11	30	18.6
Fatigue	2	4	9.5	5	5	27.8	3	4	15.0	10	13	16.9
Arthralgia	3	3	14.3	3	3	16.7	1	1	5.0	7	7	11.9
Myalgia	4	6	19.0	1	1	5.6	2	2	10	7	9	11.9

N = Number of Participants.
E = Number of Events.
All other adverse events <10% in frequency.

All of these adverse events are commonly seen in ALS patients and are expected as part of disease progression. We did not appreciate any differences in these adverse events to suggest that one form of exercise would be more likely to cause harm. The most common adverse event, overall, was falling and there was a trend towards fewer falls in the endurance and resistance exercise groups compared with SROM (Table 3).

Tolerability and compliance

Participant withdrawal and the categories for withdrawal at 12 and 24 weeks are outlined in Figure 1. Reasons for patient dropout included those lost to follow-up, adverse events, disease progression, difficulty with travel to the study site, and one participant who enrolled in another trial.

We defined tolerability to the exercise regimen based on criteria for both compliance of the regimen within each 'exercise day' as well as compliance of $\geq$50% of the total number of exercise days during the period of observation. Figure 2 shows the proportion of patients who would be compliant as a function of the compliance criteria. The dotted vertical line at 50% was the criteria we specified at the start of the trial for tolerability. At 12 weeks, the proportion of participants in the SROM group that had $\geq$50% compliance was 86% (18/21) with the resistance group at 78% (14/18) and the endurance group at 50% (10/20). At 24 weeks, the proportion of participants in the SROM group that had better than 50% compliance was 81% (17/21), with the resistance group at 68% (13/18) and the endurance group at 50% (10/20) (Figure 2). Therefore, by our predefined criteria for proportions, SROM, resistance, and endurance exercises were tolerated at both 12 and 24 weeks. Using the Proportional Hazards Model to compare the curves in Figure 2, we find that SROM was better tolerated than endurance exercise at both 12 and 24 weeks ($p = 0.01$, $p = 0.04$, respectively).

In addition to knowing the proportion of participants whose compliance was better than a predefined criterion for tolerability, we also wanted to know the average degree of compliance to exercise regimens within each study arm. In assessing exercise compliance for participants at 12 weeks, there were no differences in compliance between the SROM (76.07% $\pm$ 16.33%) and the resistance exercise group (65.23% $\pm$ 31%). Endurance exercise participants were less compliant with the protocol (50.98% $\pm$ 31.06%) compared to the SROM group ($p = 0.005$). At 24 weeks following baseline, there were no differences in compliance between the SROM group (73.22% $\pm$ 17.17%) and resistance exercise group (60.22% $\pm$ 31.11%). Endurance exercise participants showed less compliance (46.19% $\pm$ 31.1%) compared with the SROM group participants ($p = 0.01$) (Table 4).

Secondary outcome measures

We examined several measures of ALS function to determine the feasibility of performing these studies in a possible context of studying the

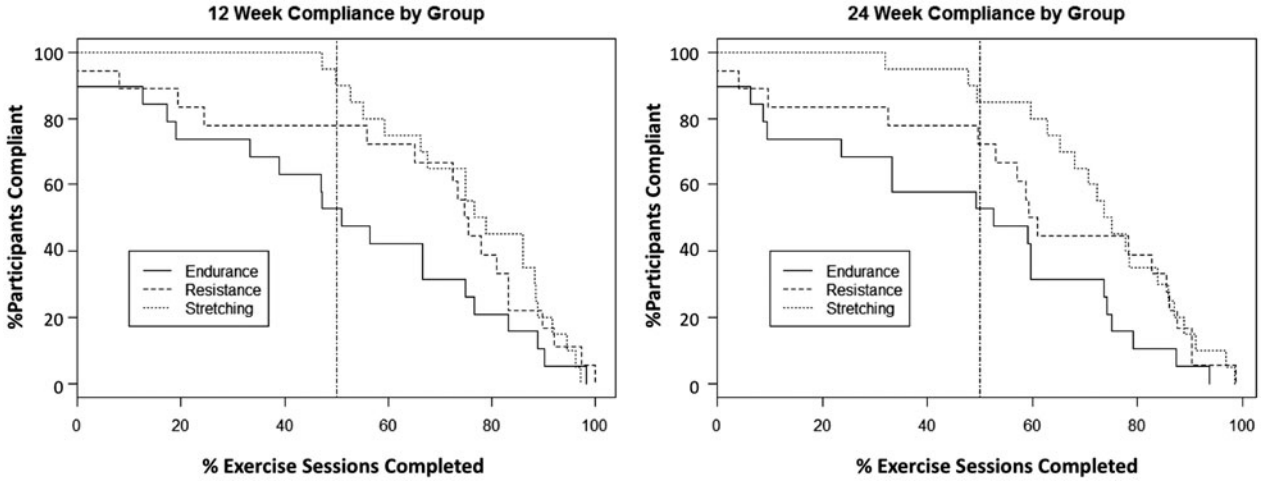

Figure 2. Proportion of tolerability to exercise at 12 and 24 weeks based upon compliance.
We used a pre-defined value of 50% compliance with the exercise regimen to inform us about tolerability and, therefore, future feasibility of performing larger efficacy studies of exercise using the prescribed regimens outlined in this study.

Table 4. Compliance.

		Randomization Groups		
	ALL $n=59$	SROM $n=21$	Resistance $n=18$	Endurance $n=20$
Compliance (12 week) (%)	64.28 ± 28.32	76.07 ± 16.33	65.23 ± 31.00	50.98 ± 31.06
Compliance (24 week) (%)	60.11 ± 28.85	73.22 ± 17.17	60.22 ± 31.11	46.19 ± 31.1
	Estimates	Std. Error	*p* value	
Comparison (12 week)				
Resistance-SROM	−10.84	8.70	0.22	
Resistance-Endurance	14.24	8.81	0.11	
SROM-Endurance	25.08	8.58	0.005	
Comparison (24 week)				
Resistance-SROM	−13.00	8.79	0.43	
Resistance-Endurance	14.03	8.89	0.38	
SROM-Endurance	27.04	8.66	0.01	

potential efficacy of exercise in ALS. The results are summarized in Supplemental Table 4. There were no differences in the slopes of decline for two of the key ALS outcome measures (ALSFRS-R and pulmonary forced vital capacity). The potential effects of all three forms of exercise on limb strength were examined by performing handheld dynamometry (HHD) on key muscle groups as well as examining grip strength. Pulmonary maximum oxygen capacity (VO_2 max) has been identified as a measure of examining endurance exercise efficacy and we did not see a difference among the groups. We were aware that exercise might result in fatigue, pain, or muscle cramps and performed measures of these elements using the fatigue severity scale (FSS) and a visual analog scale (VAS) for pain and muscle cramps. There were no increases in fatigue, pain or muscle cramps to suggest that exercise would exacerbate symptoms potentially related to both ALS and exercise. To examine the potential effects of exercise on spasticity, we incorporated the Ashworth Spasticity Scale. We did not see any differences in Ashworth Spasticity Scores among our groups. As exercise has been shown to have effects independent of those associated with muscle strength, we examined whether these exercises would change the quality of life as assessed by the ALSQoL scale. There were no differences in the quality of life measures as defined by the scale.

To assess whether the three exercise regimens studied here could cause harm compared to ALS patients who did not perform any prescribed exercise regimen, the ALSFRS-R slopes over six months from 16 trials in the PRO-ACT database were utilized for comparison (30). Our analyses suggested that none of these three prescribed exercise regimens was harmful.

Discussion

Given that 'exercise' can widely differ among individuals and that some form of physical activity is present in all individuals, we specifically sought to design a study that would allow participants the capability of exercising over several months. We also incorporated a highly prescribed regimen which would allow us to separate general physical activity from the prescribed regimen of the trial. Importantly, we also designed the study to help participants continue to exercise at appropriate levels while recognizing they would likely continue to decline physically. This enabled us to obtain a true measure of exercise effects over time and improve compliance. Because patient recall could affect an accurate measure of compliance, the design also incorporated several additional measures including exercise logs for this assessment. This afforded a less biased assessment of true compliance for both the frequency and intensity of the exercises being performed. Other factors besides intolerance to the exercise regimen or the progression of the disease itself may have contributed to compliance. Mental health, work hours, degree of family support, and other competing activities also common to healthy individuals certainly could have precluded adherence to the exercise regimens. In our secondary outcome measures, we did not identify factors that were significantly more or less common with a particular exercise regimen to suggest specific modifications.

In ALS, stretching and range of motion are routinely recommended for the prevention of 'frozen shoulder syndrome' and contractures resulting from weakness and spasticity. Therefore, maintaining an aggressive program for stretching and range of motion exercise is widely accepted as a common prescription for ALS management (7).

The studies of exercise in ALS have primarily been limited by sample size and have focused on a single form of exercise often compared with groups who received standard care in a less controlled environment where compliance can be difficult to assess but may, however, offer insights into potential utility in ALS management (22–24).

Drory et al. showed that a regular moderate physical exercise program had a short-lived positive effect on disability in ALS participants. They showed that at three months from the initiation of exercise therapy, the decline in the ALSFRS and Ashworth Spasticity Scales was improved in participants who had exercised. This effect was limited during the later time-points by the small number of participants (21).

Dal Bello-Haas et al. focused on resistance training in 13 ALS participants. They showed that the resistance exercise group had significantly better function, as measured by total ALSFRS, upper and lower extremity subscale scores, and quality of life without adverse effects compared with participants receiving standard care (25).

A more recent study by Lunetta et al. compared individuals who were prescribed 'standard care' and a second group who were under a strictly monitored exercise program (SMEP). That subgroup was further divided into individuals who performed an active exercise program plus cycloergometer activity, a second subgroup of only active exercise, and a third subgroup who performed passive exercises. They observed a difference in the ALSFRS-R in those who underwent the SMEP compared with those who had 'standard care' at a single 180-d endpoint of the study but not at earlier time-points. There were no differences in other ALS measures (31).

Using our pre-defined criteria for establishing tolerability of the prescribed exercise regimen, we have established that all three forms of exercise were tolerable for 12 and 24 weeks following enrollment into the study, but endurance exercise was less well tolerated than SROM at both time-points.

When we also examined compliance within each exercise arm at 12 and 24 weeks, compliance was highest for both SROM and resistance exercises and less so with endurance exercises. This reduced compliance could suggest that the endurance exercise regimen was too vigorous. This could be related to the time prescribed for performing the endurance exercises at each section, or possibly the frequency with which the endurance exercises occurred (3 d/week). Future trials addressing the intensity and frequency of exercise, in the course of disease progression, may help to clarify this issue.

With the current sample size it was not possible to assess treatment efficacy. Not unexpectedly, we were unable to detect a significant improvement in the slope of decline for measures of ALS function including the ALSFRS-R or pulmonary forced vital capacity. However, important to the care of ALS patients, the absence of any significant exacerbation in any of these measures would suggest that these exercises do not worsen disease progression compared with each other. More broadly, when the natural history data of ALS controls from the PRO-ACT Database were analyzed using a random slopes model of the ALSFRS-R, none of the three exercise regimens was found to be harmful to participants.

Taken together, this study demonstrates that in the short term, resistance, endurance, and SROM exercises are well tolerated and safe. At longer time-points of six months, resistance exercise is equally tolerated compared to the current care for stretching and range of motion. Importantly, we did not find that resistance or endurance exercise were harmful compared to SROM nor did they exacerbate key predictors of ALS function compared with historical ALS controls. The most common adverse event in our ALS participants overall was falling. However, participants in the endurance and resistance exercise groups had a trend towards fewer falls that may

suggest these exercise prescriptions could reduce the risk of serious injury to our patients. The results of this randomized study, comparing resistance and endurance exercise with current care for SROM, allows for these prescribed ALS exercise regimens to be incorporated into the management of ALS patients. These findings may help to enable clinicians to advise patients regarding exercise in ALS.

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Declaration of interest

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Supplementary material available online

Supplement Table 1. Resistance Exercise Protocol

Frequency	Action	Sets, repetitions, and intensity	Rest periods
3days/week	Shoulder flexion (sitting position chair or bench)	Wk 0-2: 2 sets of 8 reps at 40% 1RM Wk 3-4: 2 sets of 8 reps at 50% 1RM Wk 5-24: 2 sets of 8 reps at 70% 1RM	3-5 sec. between reps 2 min. between sets 4 min. btwn. muscle groups
	Elbow flexion (sitting position chair or bench)	Wk 0-2: 2 sets of 8 reps at 40% 1RM Wk 3-4: 2 sets of 8 reps at 50% 1RM Wk 5-24: 2 sets of 8 reps at 70% 1RM	3-5 sec. between reps 2 min. between sets 4 min. btwn muscle groups
	Elbow extension (sitting position chair or bench)	Wk 0-2: 2 sets of 8 reps at 40% 1RM Wk 3-4: 2 sets of 8 reps at 50% 1RM Wk 5-24: 2 sets of 8 reps at 70% 1RM	3-5 sec. between reps 2 min. between sets 4 min. btwn muscle groups
	Grip (Digi-Flex hand exerciser)	Wk 0-2: 2 sets of 8 reps at 40% 1RM Wk 3-4: 2 sets of 8 reps at 50% 1RM Wk 5-24: 2 sets of 8 reps at 70% 1RM	3-5 sec. between reps 2 min. between sets 4 min. btwn muscle groups
	Hip Flexion (straight leg raise) (supine position bench or bed)	Wk 0-2: 2 sets of 8 reps at 40% 1RM Wk 3-4: 2 sets of 8 reps at 50% 1RM Wk 5-24: 2 sets of 8 reps at 70% 1RM	3-5 sec. between reps 2 min. between sets 4 min. btwn muscle groups
	Knee extension (reclined position weight bench)	Wk 0-2: 2 sets of 8 reps at 40% 1RM Wk 3-4: 2 sets of 8 reps at 50% 1RM Wk 5-24: 2 sets of 8 reps at 70% 1RM	3-5 sec. between reps 2 min. between sets 4 min. btwn muscle groups
	Knee flexion (prone position weight bench)	Wk 0-2: 2 sets of 8 reps at 40% 1RM Wk 3-4: 2 sets of 8 reps at 50% 1RM Wk 5-24: 2 sets of 8 reps at 70% 1RM	3-5 sec. between reps 2 min. between sets 4 min. btwn muscle groups

Supplement Table 2. Endurance Exercise Protocol

Frequency	**Duration**	**Intensity Upper limbs**	**Intensity Lower limbs**
3 days/week	10 minutes of upper limb exercise followed by 10 min. lower limb exercise at target heart rate once daily (If subject unable to perform any upper limb or lower limb exercise then 10 min of either upper limb or lower limb exercise will be substituted) 5 minute warm-up/cool-down period.	1. Free motion at 40-70% of target HR 2. Borg scale 13-15 "somewhat hard" to "hard".	1. Free spin with 40-70% of target heart rate (heart rate reserve) 2. Borg scale 13-15 "somewhat hard" to "hard".

Supplement Table 3. Stretching and Range of Motion Exercise Protocol

Frequency	Action	Repetitions and duration	Rest periods
3 days/week	Shoulder flexion (sitting position chair or bench)	Wk 0-24: 4 repetitions Each stretch maintained 30 seconds	3-5 sec. between reps
	Triceps stretching (sitting position chair or bench)	Wk 0-24: 4 repetitions Each stretch maintained 30 seconds	3-5 sec. between reps
	Hand and Wrist stretching (sitting position chair or bench)	Wk 0-24: 4 repetitions Each stretch maintained 30 seconds	3-5 sec. between reps
	Hamstring Stretching (supine position bench or bed)	Wk 0-24: 4 repetitions Each stretch maintained 30 seconds	3-5 sec. between reps
	Quadriceps stretching (prone position)	Wk 0-24: 4 repetitions Each stretch maintained 30 seconds	3-5 sec. between reps
	Gastrocnemius stretching (supine position bench or bed	Wk 0-24: 4 repetitions Each stretch maintained 30 seconds	3-5 sec. between reps

Supplement Table 4. Secondary Outcome Measures

	Slope± S.E.			Estimate± S.E. (p-value)		
Outcome Measure	**SROM**	**Resistance**	**Endurance**	**Resistance-SROM**	**Resistance-Endurance**	**SROM-Endurance**
ALSFRS-R	-0.71±0.21	-0.97±0.23	-0.98±0.23	-0.26±0.30 (0.82)	0.01±0.32 (1.00)	0.27±0.30 (0.80)
Fasciculations (VAS)	-1.18±0.77	-0.50±0.82	-1.65±0.98	0.68±1.08 (0.92)	1.15±1.23 (0.77)	0.48±1.20 (0.98)
Muscle Pain (spontaneous)	-0.22±0.92	0.32±0.99	-0.22.±1.14	0.10±1.25 (1.00)	0.54±1.41 (0.98)	0.43±1.37 (0.99)
Muscle Cramps During Exercise	-0.04±0.64	-0.08±0.68	-1.14±0.81	-0.04±0.89 (1.00)	1.06±1.02 (0.71)	1.09±0.99 (0.67)
Muscle Stiffness	-0.03±0.74	0.45±0.78	0.36±0.93	0.47±1.04 (0.97)	0.08±1.18 (1.00)	-0.39±1.15 (0.99)
Ashworth Spasticity Scale	0.01±0.02	-0.009±0.02	-0.02±0.02	-0.02±0.03 (0.80)	0.007±0.03 (0.99)	0.03±0.03 (0.67)
Fatigue Total Score	0.59±0.45	0.95±0.50	0.45±0.57	0.36±0.67 (0.95)	0.51±0.75 (0.90)	0.15±0.73 (1.00)
Fatigue Severity Scale	0.07±0.05	0.11±0.06	0.05±0.06	0.04±0.07 (0.95)	0.06±0.08 (0.90)	0.02±0.08 (1.00)
Grip Strength Megascore	-5.70±1.02	-3.71±1.10	-4.25±1.27	1.98±1.47 (0.51)	0.54±1.64 (0.99)	-1.44±1.59 (0.79)
HHD Upper Ext. Megascore	-4.14±0.90	-3.74±0.97	-5.15±1.04	0.40±1.32 (0.99)	1.41±1.43 (0.73)	1.01±1.37 (0.87)
HHD Lower Ext. Megascore	-2.43±0.90	-1.93±0.98	-3.24±1.09	0.49±1.32 (0.98)	1.30±1.46 (0.79)	0.81±1.41 (0.93)
VO2 testing predicted	-0.01±0.01	0.01±0.01	0.02±0.01	0.01±0.01 (0.68)	-0.01±0.01 (0.92)	-0.02±0.01 (0.35)
ALS QOL predicted	-0.07±0.03	-0.13±0.03	-0.04±0.04	-0.06±0.04 (0.46)	-0.09±0.05 (0.24)	-0.03±0.05 (0.92)
VC predicted	-2.12±0.62	-2.18±-.66	-2.55±0.77	-0.06±0.91 (1.00)	0.36±1.01 (0.98)	0.42±0.99 (0.97)