ORIGINAL ARTICLE

# Supported Treadmill Ambulation for Amyotrophic Lateral Sclerosis: A Pilot Study

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ABSTRACT. Sanjak M, Bravver E, Bockenek WL, Norton J, Brooks BR. Supported treadmill ambulation for amyotrophic lateral sclerosis: a pilot study. Arch Phys Med Rehabil 2010; 91:1920-9.

**Objectives:** To determine the feasibility, tolerability, safety, and exercise treatment-effect size of repetitive rhythmic exercise mediated by supported treadmill ambulation training (STAT) for patients with amyotrophic lateral sclerosis (ALS).

**Design:** Interventional with repeated-measures design.

**Setting:** Multidisciplinary ALS clinic at academic medical center.

**Participants:** Convenience sample of patients with ALS (N=9) who were ambulatory with assistive devices (Sinaki-Mulder stages II–III).

**Interventions:** Repetitive rhythmic exercise-STAT (30min total; 5min of exercise intercalated with 5min of rest) performed 3 times a week for 8 weeks.

**Main Outcome Measure:** ALS Functional Rating Scale-Revised (ALSFRS-R), percentage of predicted vital capacity (VC), total lower-extremities manual muscle test (MMT), rate of perceived exertion (RPE), Fatigue Severity Scale (FSS), and maximum voluntary isometric contraction (MVIC) in 10 lower and 10 upper extremities. Gait performance, which included walking distance, speed, steps, and stride length, was evaluated during treadmill and ground 6-minute walk tests (6MWTs) and 25-foot walk test (25FWT).

**Results:** Feasibility issues decreased screened participants by 4 patients (31%). Nine patients were enrolled, but 6 patients (67%) completed the study and 3 (23% of original cohort; 33% of enrolled cohort) could not complete the exercise intervention because of non–ALS-related medical problems. Tolerability of the intervention measures during the treadmill 6MWT showed improvement in RPE ($P\leq.05$) and FSS score ($P\geq.05$). Safety measures (ALSFRS-R, VC, MMT) showed no decrease and showed statistical improvement in ALSFRS-R score ($P\leq.05$) during the study interval. Exercise treatment-effect size showed variable improvements. Gait speed, distance, and stride length during the treadmill 6MWT improved significantly ($P\leq.05$) after 4 weeks and improvements were maintained after 8 weeks compared with baseline. Walking distance during the ground 6MWT increased significantly after 4 weeks and was maintained after 8 weeks compared with baseline ($P\leq.05$). Walking speed during the 25FWT and lower-extremity MVIC improved, but were not statistically significant.

**Conclusions:** Repetitive rhythmic exercise-STAT is feasible, tolerated, and safe for patients with ALS. Repetitive rhythmic exercise-STAT treatment-effect size across a number of ALS-related measures was consistent with improved work capacity and gait function in patients with ALS who are dependent on assistive devices for ambulation. Repetitive rhythmic exercise-STAT should be evaluated further in larger studies to determine the stability of this improved function in relation to the rate of progression of the underlying ALS.

**Key Words:** Amyotrophic lateral sclerosis; Gait; Rehabilitation.



AMYOTROPHIC LATERAL sclerosis is a progressive fatal neurodegenerative disorder characterized by selective loss of upper and lower motor neurons in the cerebral cortex, brainstem, and spinal cord. ALS leads to progressive muscular weakness and atrophy of limb, bulbar, and respiratory musculature; fatigue; loss of balance; and spasticity.[1] Currently, there is no cure for ALS. Riluzole, a glutamate antagonist, the only approved medication to treat ALS, has effects on survival (2–3mo delay to ventilator use or death) with no effect on function.[2]

Recent evidence-based American Academy of Neurology Practice Parameter (parameters) Updates for ALS[3,4] reported that, in addition to limited medical treatment and management

**List of Abbreviations**

| | |
|---|---|
| 6MWT | six-minute walk test |
| 25FWT | 25-foot walk test |
| ALS | amyotrophic lateral sclerosis |
| ALSFRS-R | ALS Functional Rating Scale-Revised |
| BiPAP | bilevel positive airway pressure |
| FSS | Fatigue Severity Scale |
| MMT | manual muscle test |
| MVIC | maximum voluntary isometric contraction |
| RPE | rate of perceived exertion |
| $SaO_2$ | oxygen saturation, arterial |
| STAT | supported treadmill ambulation training |
| VC | percentage of predicted vital capacity |

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strategies, few supportive measures are available that may be beneficial as treatment to slow progression and improve survival and quality of life. According to the parameters, noninvasive assisted ventilation, assisted feeding by means of percutaneous endoscopic gastrostomy, and assisted coughing were effective in the management of ALS.[3] The parameters mentioned therapeutic exercise as a potential intervention for the management of spasticity in patients with ALS,[4] but recommended further research on the effects of exercise on ALS disease management and progression because of insufficient evidence.[5-7]

The role of therapeutic physical exercise in the management and treatment of patients with ALS is controversial.[8-12] A few studies have shown modest effects of moderate exercise in improving scores on functionality tests and decreasing disease symptoms,[13-17] but none have shown an effect on ambulation. Exercise parameters, such as type, mode, and dosing (duration, frequency, and intensity), were not clearly defined in these studies.

Lack of strong evidence of benefits of regular exercise has led many clinicians to discourage patients with ALS from engaging in regular physical exercise because of a general belief that physical strain might be harmful and aggravate motor neuron demise, leading to the risk for overwork weakness.[8,18-22]

However, decreased physical activiy will lead to deconditioning with significant physical (fraility) and psychological comorbid conditions.[23,24] The extent to which deconditioning and disuse atrophy contribute to the observed motor impairments seen in patients with ALS is not clear.

Conversely, regular repetitive rhythmic exercise has positive health outcomes in the general population,[25] including older adults[26] and persons with neurodegenerative disease.[27-30] Consistent and compelling evidence has shown that repetitive rhythmic exercise improves cardiovascular fitness, neuromuscular function, immune system function, mobility, balance, bone density, cognitive function, and mood while decreasing secondary disease symptoms, such as fatigue, depression, and fall risk.[24-30]

Patients with ALS who are ambulatory with the use of assistive devices (Sinaki-Mulder stages II–III)[10] may not be able to engage in functional repetitive rhythmic exercise with the intensity and duration needed to appropriately produce physiologic and neurologic effects without assistance. This may be caused by the inability to generate adequate force to move their entire body weight from one place to another because of weakness, fatigue, incoordination, spasticity, imbalance, and/or fear of falling. Subsequently, ambulatory patients with ALS are forced to adapt to a more sedentary lifestyle to accommodate for difficulties and risks associated with ambulation. These barriers may deprive patients of the opportunity to engage in regular repetitive rhythmic exercise to receive the necessary amount of exercise dose needed for proper activation of the neuromuscular system and promote the conditioning, neuronal plasticity, and neuroprotection associated with exercise.

STAT is a suitable and innovative approach that acts as an assistive device. It may enable such patients to engage in safe functional repetitive rhythmic exercise gait training.[31,32] Reducing body weight will decrease the biomechanical, physiologic, and metabolic requirement imposed on a patient's musculoskeletal and cardiopulmonary systems. Subsequently, STAT may allow patients with ALS who could not freely ambulate in a rhythmic repetitive fashion to do so and to progressively increase their stepping frequency and duration and protect patients from overwork injuries, deconditioning, and disuse atrophy. Repetitive rhythmic exercise in the form of gait, mediated by STAT (repetitive rhythmic exercise-STAT) has been shown to be an effective treatment that improved gait speed, cadence, stride length, gait symmetry, interlimb coordination during gait, balance, and endurance for persons with a variety of neurologic deficits leading to walking disability.[31-39] Its efficacy to improve gait and work capacity has been shown in patients with traumatic brain injury,[33] spinal cord injury,[34,35] cerebral palsy,[36] stroke,[37] progressive supranuclear palsy,[38] Parkinson's disease,[39] and multiple sclerosis,[40] but has not been used previously in patients with ALS.

In addition, repetitive rhythmic exercise-STAT may enable patients to receive the necessary amount of exercise needed for proper activation of the neuromuscular system to promote the neuronal plasticity and neuroprotection associated with exercise in healthy human[41] and animal models of ALS.[42-46]

The purpose of this pilot study was to determine the feasibility, tolerability, safety, and efficacy of 8 weeks (24 sessions) of active assisted, mild to moderate intensity repetitive rhythmic exercise-STAT on gait function, muscle strength, fatigue, vital capacity, and daily activity function in patients with ALS who are ambulatory with assistive devices (Sinaki-Mulder stages II–III).[10]

## METHODS

Individuals (N=13) with a clinically definite diagnosis of ALS according to the modified El Escorial criteria[47] were screened for this pilot study in accordance with Carolinas Medical Center Internal Review Board–approved procedures. Participation was offered to a convenience sample of patients who attended the Carolinas Neuromuscular/ALS-MDA Center for their usual clinical care. Inclusion criteria were as follows:

**Table 1: Patient Demographics**

| Patient No. | Sex | Age (y) | Height (cm) | Weight (kg) | BMI ($m^2$) | Assistive Device Used |
|---|---|---|---|---|---|---|
| 001 | F | 58 | 163 | 50 | 19 | Bi AFOs, 4WW, PWC |
| 002 | F | 41 | 173 | 68 | 23 | L AFO |
| 003 | F | 61 | 155 | 63 | 27 | Bi AFOs, 4WW, PWC |
| 004 | M | 39 | 188 | 92 | 26 | Bi AFOs |
| 005 | M | 72 | 185 | 83 | 26 | 4WW, BiPAP |
| 006 | M | 77 | 178 | 68 | 22 | Bi AFOs, 4WW |
| 007 | F | 68 | 170 | 67 | 23 | 4WW |
| 008 | M | 65 | 168 | 70 | 25 | Bi AFOs |
| 009 | F | 77 | 165 | 56 | 19 | Bi AFOs, BiPAP |

Abbreviations: 4WW, 4-wheeled walker; AFO, ankle foot orthosis; Bi AFO, bilateral ankle-foot orthosis; BMI, body mass index; L, left; PWC, power wheelchair.

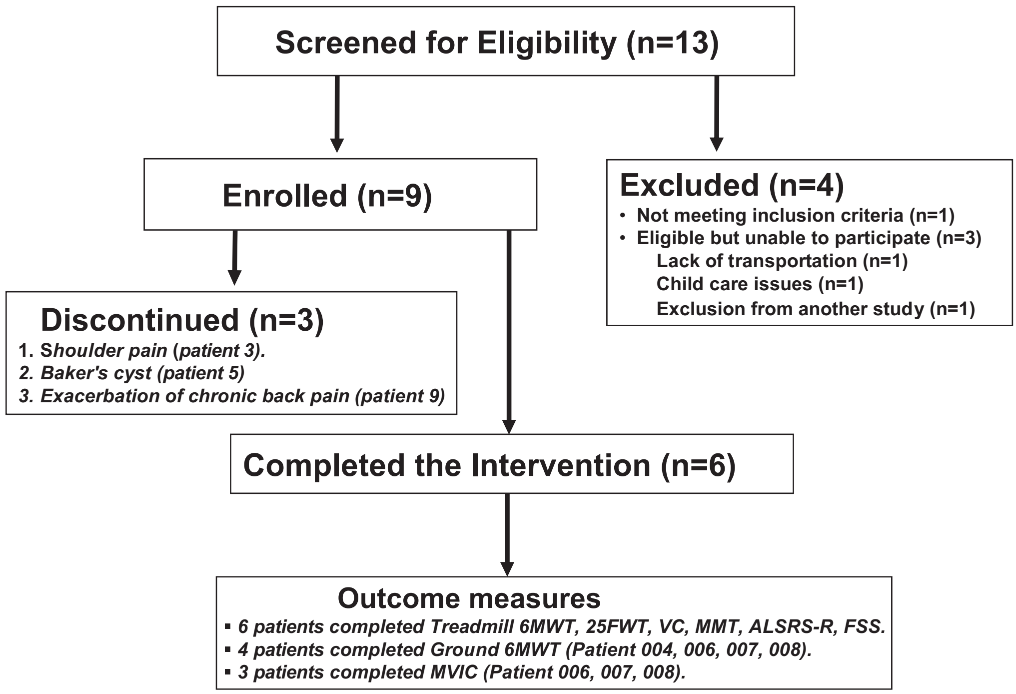


Fig 1. Flow chart procedures.

definite diagnosis of ALS/motor neuron disease, ambulatory with the aid of assistive devices (such as walker, cane, or ankle-foot orthosis), aged 25 to 80 years, able to walk 25 feet in 1 minute or less, VC of 50% or greater, and able to provide informed consent. Enrolled patients demographics are shown in table 1.

### Procedures

The exercise intervention consisted of 8 weeks of repetitive rhythmic exercise-STAT. Patients exercised 3 times a week on nonconsecutive days for 24 training sessions. During each visit, patients walked on a Biodex Gait Trainer II Treadmill with overhead Biodex unweighting system[a] with up to 40% of their body weight supported. Unloading of the lower extremities (40%) resulted in straighter trunk and knee alignment during the loading phase, a decrease in double support time, and an increase in single support time, stride length, and speed compared with 0% body weight support.[37] The 60-minute training session consisted of 6 intervals of 5 minutes of exercise interspersed with 5 minutes of rest to avoid overwork weakness and fatigue. Patients were allowed to hold on to the handrail for balance only. A physical therapist supervised all patients individually on all exercise sessions. The therapist did not provide manual assistance to improve performance or intralimb kinematics, but focused on monitoring the patient's level of exertion and adjusting intensity by changing treadmill speed and

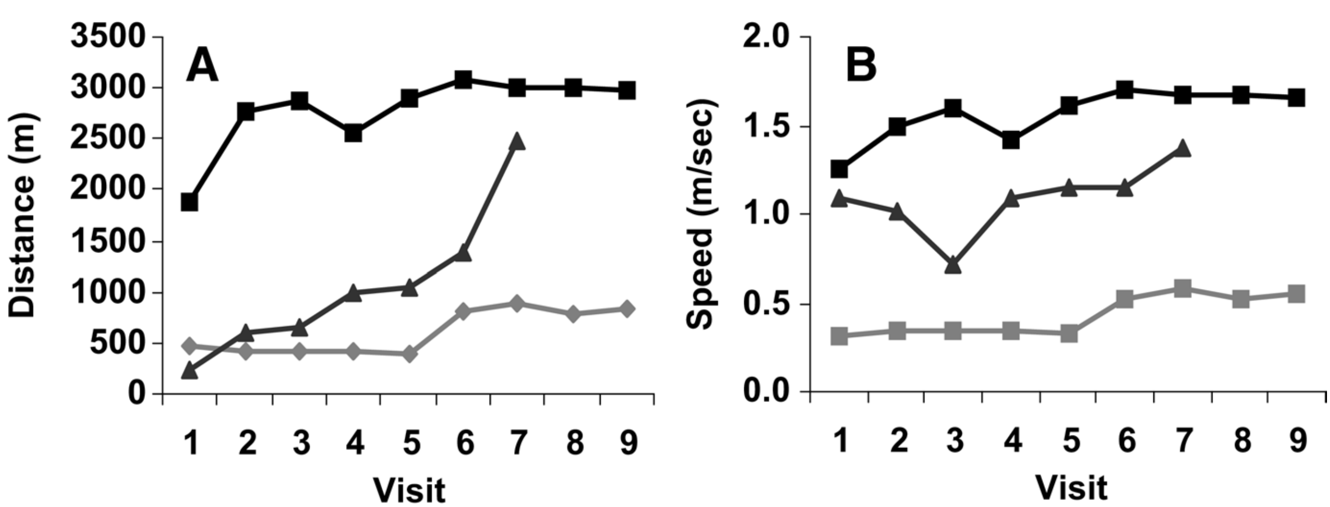


Fig 2. (A) Total walking distance and (B) average speed achieved at each visit in patients who discontinued the study.

Table 2: Tolerability Outcome Measures

| Outcome | Baseline | 4 wk | 8 wk | *P* |
|---|---|---|---|---|
| RPE | 15.0±3.5 | 9.8±4.1 | 8.1±3.5 | .0225* |
| FSS score | 36.0±11 | 26.0±15 | 25.8±15 | .4666 |

NOTE. Values shown are mean ± SD.
*Statistically significant difference.

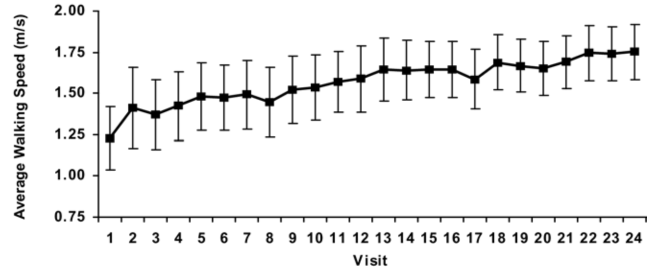


**Fig 4. Average walking speed achieved at each visit in patients who completed the study. Values shown as mean ± SE.**

amount of stepping practice, as tolerated. Exercise intensity was guided by each patient's own RPE, but was not to exceed level 12 to 13 (moderate) on the modified Borg perceived exertion scale.[48] Walking speed was determined as tolerated by each patient's own stepping pace. Visual and auditory feedback of patients' step length and frequency was shown on a monitor connected to the treadmill, producing computer-generated messages to adjust step length to achieve proper gait cycle and symmetry. A 5-minute exercise interval was sufficient for patients to reach a steady state of repetitive rhythmic exercise for proper dosing and adaptation.[49] Five minutes of rest was provided to reduce the effect of fatigue in these patients.[50]

Patients who used intermittent BiPAP were fitted with volume-based BiPAP during the exercise periods. During exercise, $SaO_2$ was monitored by using pulse oximetry to ensure that $SaO_2$ was maintained at 90% or greater for all patients. For the 2 patients using BiPAP, oxygen was supplemented as needed to maintain $SaO_2$ at 90% or greater.

## Outcome Measures

***Feasibility of repetitive rhythmic exercise-STAT.*** Feasibility was evaluated as the percentage of patients screened to percentage enrolled in the study and the percentage of patients enrolled to percentage that completed the study.

***Tolerability of repetitive rhythmic exercise-STAT.*** Tolerability was evaluated by using percentage of change in RPE during the 6MWT on a treadmill performed under conditions similar to the training period with 40% of body weight supported, FSS score,[51] and progression of training load (distance and average speed) during each visit.

***Safety of repetitive rhythmic exercise-STAT.*** Safety was evaluated by means of change in the ALSFRS-R score,[52] VC,[53] and total bilateral lower-extremity muscle strength evaluated by using the MMT.[54] VC was measured using a portable Puritan-Bennett Renaissance II Spirometry System[b] connected to uni-directional flow sensors (Pneumo-Tach, FS 200).[b] Patients were instructed to take the longest deepest breath possible and blow it out completely in a relaxed (not forceful) manner. MMT in the ankle, knee, hip flexors/extensors, and hip adductors/abductors was evaluated following standard procedures.[53] ALSFRS-R, VC, and MMT commonly are used to evaluate disease progression and as efficacy outcome measures in ALS clinical research.[55]

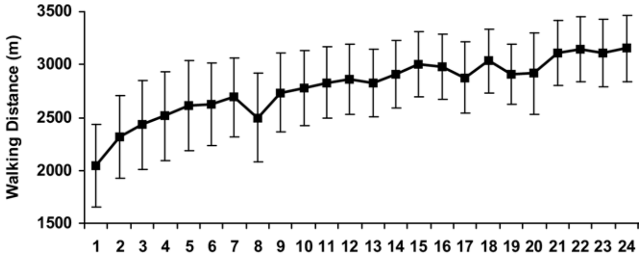


**Fig 3. Total walking distance achieved at each visit in patients who completed the study. Values shown as mean ± SE.**

***Treatment-effect size of repetitive rhythmic exercise-STAT.*** Treatment-effect size was evaluated by means of changes in gait performance during the 6MWT on a treadmill and on the ground, 25FWT, and change in muscle strength using MVIC.

Distance, average speed, and step length during the treadmill 6MWT were evaluated under conditions similar to those during the training period of 40% of body weight supported. The treadmill was equipped with 4 strain gauges under the belt that are sensitive to bending of the belt caused by the weight applied by the patient walking. These gauges are connected to software that enables the user to produce a report summarizing the patient's performance, including distance, average speed, step length, step speed, and right-to-left time distribution (step symmetry). Patients were instructed to walk as fast as they could for 6 minutes. Treadmill speed was adjusted to each patient's maximum walking speed or to the maximum treadmill walking speed set on the gait mode to avoid running. The patient's RPE were collected each minute; the highest score was used as part of tolerability analysis.

Distance achieved during the ground 6MWT was recorded following a standardized protocol.[56] Patients were instructed to walk as far as they could for 6 minutes on a flat hard surface wearing shoes and using their usual assistive devices around a track of a 40-m hallway. Patients were instructed to stop and rest during the test if they needed to and resume walking as soon as they were able until the 6 minutes were completed. The 6MWT has been validated by high correlation with workloads, heart rate, $SaO_2$, and dyspnea responses compared with standard bicycle ergometry and treadmill exercise tests.[56] The 6MWT is simple, reproducible, safe, inexpensive, applicable to everyday activities, sensitive to therapeutic interventions, and of prognostic relevance.[57,58] It has been used increasingly in patients with a variety of neurologic disease, including Alzheimer disease,[59] Duchenne muscular dystrophy,[60] myotonic dystrophy,[61] and ALS.[62]

Table 3: Safety Outcome Measures

| Outcome | Baseline | 4 wk | 8 wk | *P* |
|---|---|---|---|---|
| ALSFRS-R score | 34±5 | 38±6 | 37±6 | .022* |
| VC (%) | 88±16 | 92±17 | 93±19 | .433 |
| MMT† | 62±12 | 65±13 | 67±13 | .096 |

NOTE. Values shown are mean ± SD.
*Statistically significant difference from baseline.
†Total lower-extremity score.

**Table 4: Treatment Effect Size**

| Outcome Measures | Baseline | 4 wk | 8 wk | *P* |
|---|---|---|---|---|
| Treadmill 6MWT | | | | |
| Distance (m) | 465±165 | 632±157* | 667±146† | .0296 |
| Average speed (m/s) | 1.43±0.5 | 1.77±0.4* | 1.84±0.4† | .0481 |
| Average left step length (m) | 0.85±0.3 | 1.07±0.2 | 1.12±0.1 | .0502 |
| Average right step length (m) | 0.79±0.2 | 1.15±0.1 | 1.14±0.1 | .0602 |
| Stride length (m) | 1.6±0.5 | 2.2±0.2* | 2.3±0.2† | .0108 |
| Ground 6MWT distance (m) | 440±91 | 532±73* | 533±72† | .0382 |
| 25FWT speed (ft/s) | 3.7±1.6 | 4.3±1.8 | 4.7±1.9 | .0759 |
| MVIC (% predicted) | | | | |
| Lower extremities | 87.5±7 | 93.0±12 | 92.2±10 | .0939 |
| Upper extremities | 88.7±18 | 102.5±19 | 98.93±18 | .0820 |

NOTE. Values shown are mean ± SD.
*Statistically significant differences at 4 weeks.
†Statistically significant difference at 8 weeks compared with baseline.

Gait speed was evaluated during the 25FWT**.** Patients were timed walking a measured 25 feet as fast and as safely as possible, using their assistive devices. Time was calculated from the initiation of walking and ended when the patient crossed the 25-foot mark. The 25FWT is a quantitative mobility and leg function test. It is an accurate measure of ambulation that reflects daily activity measured by using a step activity monitor accelerometer in patients with Friedreich ataxia.[63] The 25FWT has been used as an outcome measure in patients with a variety of neurologic conditions and has high interrater and test-retest reliability and concurrent validity.[64]

MVIC of 10 upper- and 10 lower-extremity muscles was evaluated by using a computerized force measurement system using a force transducer (Interface SM-250).[c65] MVIC has been validated and used in ALS clinical trials. Its reliability and sensitivity have been validated by several natural history studies.[1,66]

### Statistical Analysis

Descriptive statistics, including mean ± SD or count and percentage, were calculated. Because each subject was measured at 3 times, repeated-measures analysis of variance was used. If the *P* value from the repeated-measures analysis of variance was significant, paired *t* tests were used to compare times 2 at a time by using the Bonferroni-Holm correction for multiple comparisons. Because all *P* values that were significant also were significant by using Bonferroni-Holm, unadjusted *P* values are reported. SAS software[d] was used for all analyses. A 2-tailed $P<.05$ was considered statistically significant.

## RESULTS

### Feasibility Outcome Measure

Of the patients (n=13) screened, 1 did not meet the inclusion criteria and 3 eligible patients (23%) could not enroll because of a variety of issues (fig 1).

Six (67%) of the 9 enrolled patients completed the study. This percentage is better or equivalent to other home exercise studies performed with patients with ALS. Our supervised study is more time demanding and required patients to travel 3 times a week to receive the intervention. Two patients who completed the study traveled for more than 1 hour each way. Adherence to the appointment schedule was excellent. All patients, including dropouts, had a positive experience with the

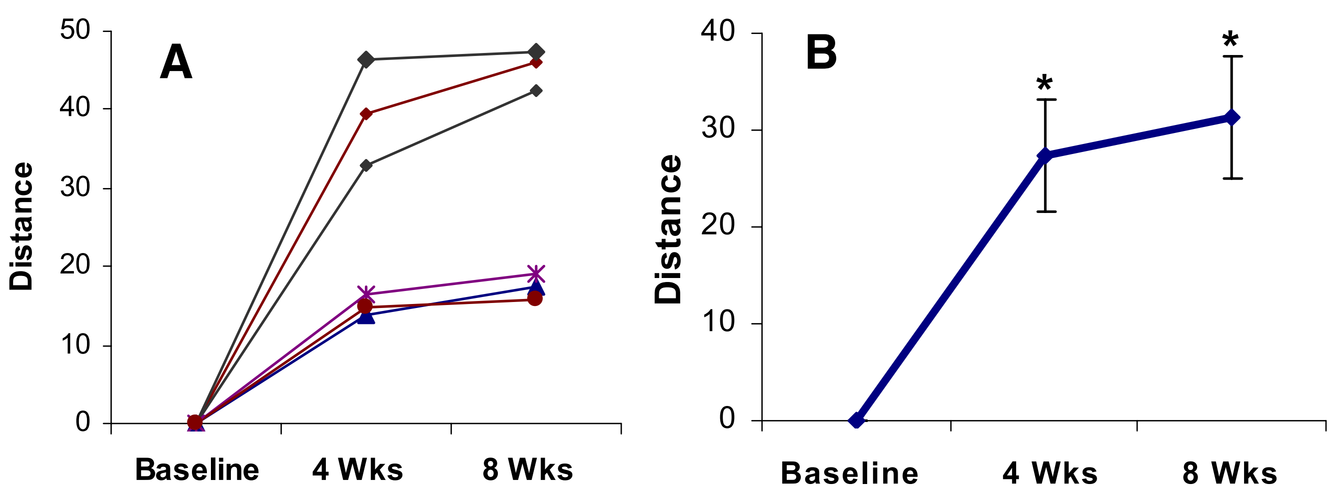


**Fig 5. Percentage of change in treadmill 6MWT distance for (A) each participant and (B) mean ± SE values. *Significant difference at 4 and 8 weeks (*P*≤.05) compared with baseline.**

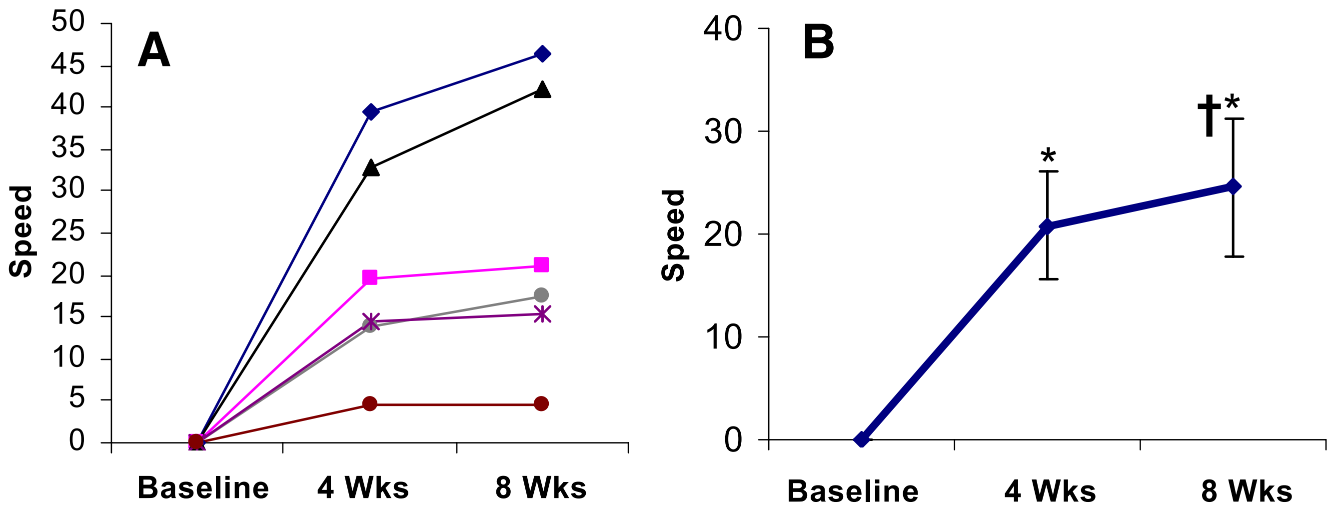


**Fig 6. Percentage of change in treadmill 6MWT average walking speed for (A) each participant and (B) mean ± SE values. *Significant difference at 4 weeks. †*Significant difference at 8 weeks ($P \leq .05$) compared with baseline.**

intervention. Patients who completed the study expressed the desire to continue the intervention.

Three patients (33%) could not complete the exercise intervention because of orthopedic issues that interfered with gait training. One patient (patient 3) dropped out after 9 visits because of right shoulder pain, this patient use a power wheelchair for community ambulation. The second patient (patient 5) dropped out after 6 visits because of a left-knee Baker cyst. The third (patient 9) dropped out after 9 visits because of exacerbation of chronic low-back pain. Patients 5 and 9 were BiPAP users and, as stated, they dropped out of the study because of orthopedics limitations and not because of exercise intolerance or breathing difficulties. Training walking distance and average speed achieved by these dropout patients are shown in figure 2. The data show that patient dropout was not caused by deterioration in performance. Patients who dropped out expressed regrets and wanted to continue after recovery, but time limitation could not allow for it.

### Tolerability Outcome Measures

RPE significantly decreased at 4 and 8 weeks ($P \leq .05$) compared with baseline. FSS scores also decreased at 4 and 8 weeks, but this was not statistically significant (table 2). These findings indicate improvement in the perception of exertion and the general feeling of fatigue despite the higher work load achieved during the 8 weeks of repetitive rhythmic exercise-STAT (figs 3 and 4).

### Safety Outcome Measures

Safety measures showed no decline during the study period. There was a statistical increase in ALSFRS-R scores at 4 weeks

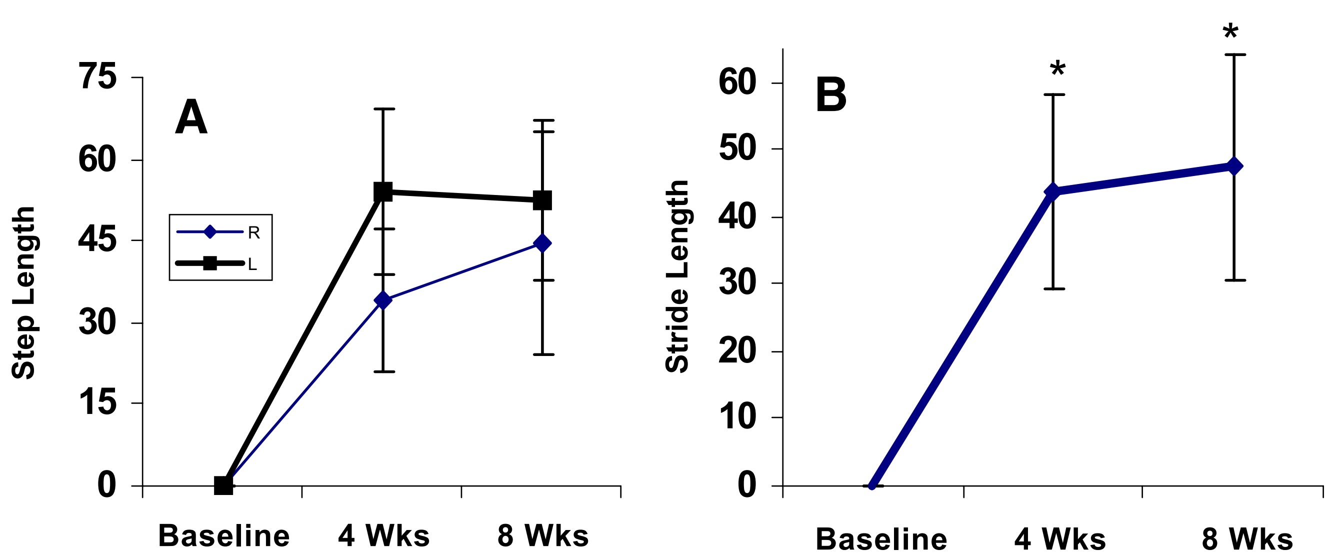


**Fig 7. Percentage of change in treadmill 6MWT (A) step length and (B) stride length. *Significant difference ($P \leq .05$). Abbreviations: L, left; R, right.**

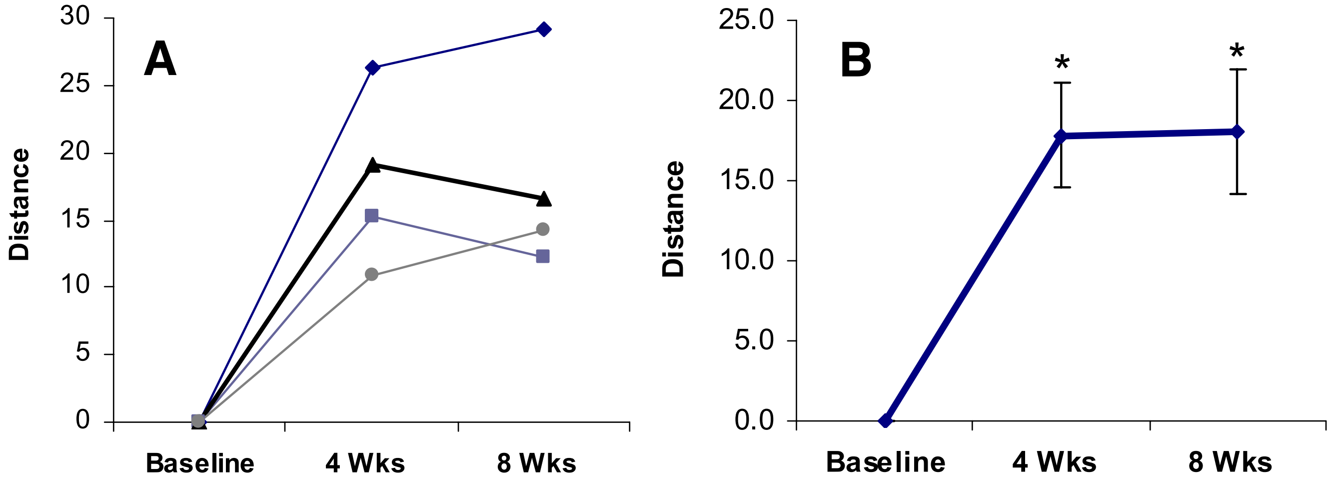


**Fig 8. Percentage of change in ground 6MWT distance for (A) each participant and (B) mean ± SE values. *Significant difference at 4 and 8 weeks ($P \leq .05$) compared with baseline.**

that was maintained at 8 weeks ($P \leq .05$) (table 3). The data indicate that repetitive rhythmic exercise-STAT is safe and did not induce a deleterious effect on disease-specific indicators commonly used to monitor progression of ALS. The predictable decrease in these outcome measures was arrested during the 2 months of exercise. Mean decreases a month were reported to be .77 to 1.07 for the ALSFRS-R score, 1.04% to 2.46% for VC, and 1.18 for MMT.[55] No adverse events related to the intervention have occurred.

### Treatment-Effect Size

Patients' gait performances during the treadmill 6MWT are listed in table 4 for the raw data and shown in figures 5 to 7 as percentage of change from baseline for each patient (figs 5A, 6A, 7A) and as group (mean ± SE) (figs 5B, 6B, 7B). Repetitive rhythmic exercise-STAT resulted in a statistically significant increase ($P \leq .05$) in walking distance and speed at 4 weeks and was maintained after 8 weeks. Stride length increased significantly at 4 weeks and was maintained at 8 weeks. Left and right step length and stride length increased, approaching statistical significance ($P = .0503$) at 4 weeks, and was maintained at 8 weeks.

Data for patients' gait performance during the ground 6MWT are listed in table 4 for raw data and as percentage of change from baseline in figures 8 and 9 for each patient (figs 8A, 9A) and as group (mean ± SE) (figs 8B, 9B). Repetitive rhythmic exercise-STAT resulted in improvement in walking distance after 4 weeks and was maintained after 8 weeks compared with baseline ($P \leq .05$).

Walking speed during the 25FWT at 4 and 8 weeks increased, but was not statistically significant.

Total upper- and lower-extremity MVIC increased after 4 weeks and stayed higher than baseline after 8 weeks (fig 10; table 4), but was not statistically significant.

## DISCUSSION

In this pilot study, repetitive rhythmic exercise-STAT over 8 weeks was feasible, tolerated, and safe and elicited improvements in gait function and work capacity in patients with ALS who use assistive devices for ambulation (stages II–III). Im-

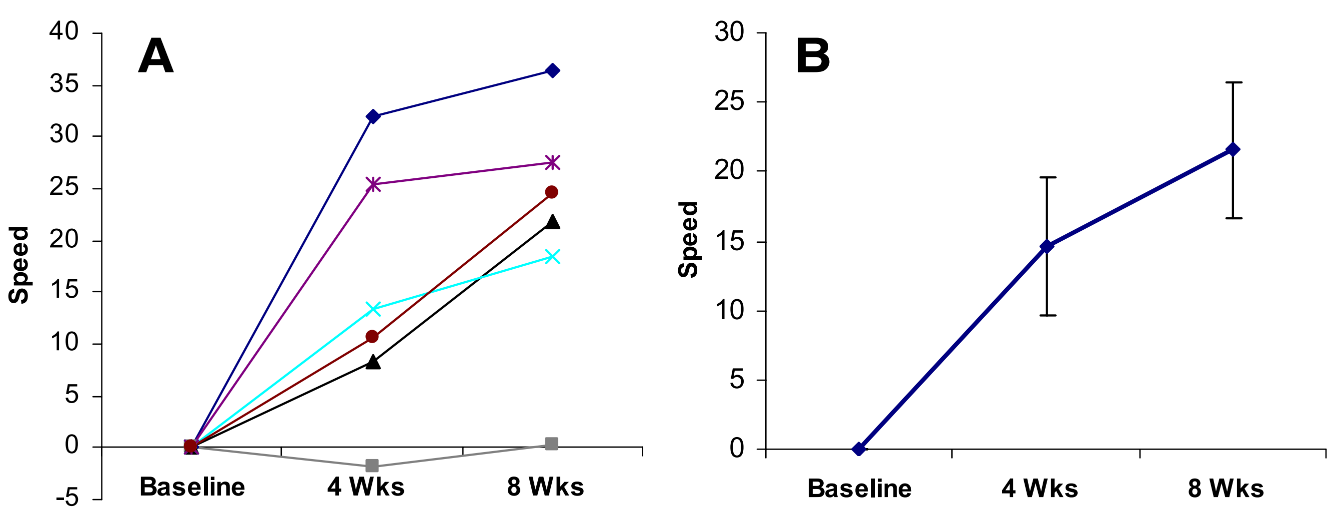


**Fig 9. Percentage of change in 25FWT walking speed for (A) each participant and (B) mean ± SE values.**

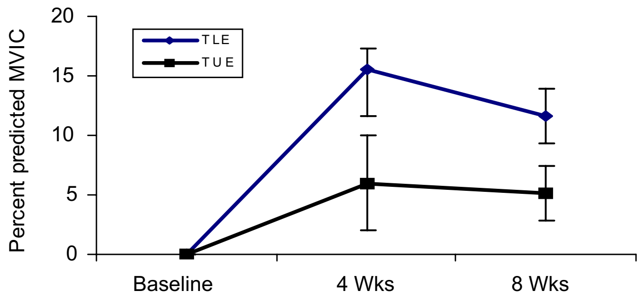


**Fig 10. Percentage of change in TUE and TLE MVIC. Values shown are mean ± SE. Abbreviations: TLE, total lower extremity; TUE, total upper-extremity.**

provements in gait function were seen after 4 weeks and maintained up to 8 weeks. The effect of repetitive rhythmic exercise-STAT was shown on several gait parameters, including distance, speed, and step and stride length during treadmill and ground walking (see table 4; figs 5–9). The average 93-m increase in ground 6MWT distance, which amounted to a 23% increase over 8 weeks, exceeded the minimal clinically important difference of 25m or 14% increase from baseline, as reported in the literature.[67]

Our preliminary data showed that ambulatory patients with ALS can show measurable training responses to functional training. Improvement in gait function in response to ambulation training is consistent with the concept of specificity of training paradigm established in exercise training science. Rehabilitation paradigms indicate that functional outcomes improve when a specific task is practiced repeatedly, rather than nonspecific interventions.[31,32] Repetitive rhythmic exercise-STAT is specific functional gait training that focuses on the entire body system and targets multiple motor outcomes, such as rhythmic stepping, strength, endurance, postural reflexes, and balance, leading to improvement in gait function.

The mechanism by which active assisted repetitive rhythmic exercise-STAT has this robust effect on improving gait function and work capacity of patients with ALS is not completely clear and needs to be investigated further in a larger clinical trial of longer duration. Two mechanisms may have contributed to this improvement.

First, the unweighting aspect of the repetitive rhythmic exercise-STAT may have protected patients from overwork weakness and allowed them to improve gait pattern and increase the amount and intensity of stepping practice to produce a training effect. This submaximal low to moderate intensity type of training primarily involves motor units innervating the slow type I muscle fibers. It may spare the fast-contracting motor units that are more severely affected than the slowly contracting motor units in these patients.[50,68] Observations from exercise studies in animal model of ALS showed that low to moderate treadmill running speed (3.4–16m/min) improved survival and delayed the onset of motor deficit,[42-46] whereas intense treadmill running speed (>22m/min) decreased survival and hastened motor function deficit.[45,69] In addition, wheel running, which is a discontinuous, nonexhaustive, noneccentric exercise, resulted in a significant increase in life span compared with sedentary animals living in cages.[45,46] Swimming, an “unweighted” activity, significantly delayed disease onset and spinal motoneuron death, preserved astrocytes and oligodendrocytes, and increased survival in an ALS mouse model compared with treadmill running.[42]

Second, the effectiveness of repetitive rhythmic exercise-STAT to improve gait in patients with ALS may be supported by research on spinal mechanisms in animals and humans. The generation of cyclic locomotor patterns can be attributed to rhythmic neural activity produced by central pattern generators in the brainstem and/or spinal cord.[70] Kittens in which the spinal cord were transected at the low thoracic level 1 week after birth were able to walk 2 days later when their hind limbs were held on a treadmill.[71] The importance of STAT may relate to its ability to provide adequate locomotor-related sensory input necessary to activate the spinal locomotor circuitry. Such input can either block or induce switching between the alternating flexor and extensor locomotor bursts,[72-75] emphasizing the tight link between sensory input and neural locomotor circuitry. There are 3 main sensory sources that satisfy these criteria; 2 are related to load and the third is related to hip position.[72-75] The 2 types of load receptor input come from proprioceptive afferents in extensor muscles and exteroceptive afferents from mechanoreceptors in the foot. The afferents signaling hip joint position come from muscles around the hip. The role of afferent activity for rhythmic locomotor patterns therefore is essential to help shape the pattern, control phase transitions, and reinforce ongoing gain and central pattern generators activity. Patients with ALS who rely on assistive devices may not be able to generate sufficient afferent rhythmic locomotor patterns without motorized treadmill and body weight support to be able to engage in functional rhythmic activities without the body weight support.

## Study Limitations

Limitations include (1) the small number of subjects, (2) limitation of study design to nonrandom treatment assignment single case pre-post treatment outcomes, and (3) no concurrent control group. The positive treatment effect size observed in this pilot study needs to be confirmed in a larger number of patients that represent different presentations of ALS such as upper vs lower motor neuron predominant disease. In addition, starting exercise treatment before there is a need for assistive devices. Further testing is required to explore the effects of this intervention on other neurophysiological and metabolic functions, as well as quality of life, in order to customize the ideal clinical parameters that will allow measurement of its usefulness for ALS patients in the clinical setting.

## CONCLUSIONS

Repetitive rhythmic exercise-STAT is feasible, tolerated, and safe for patients with ALS. Repetitive rhythmic exercise-STAT treatment-effect size across a number of ALS-related measures is consistent with improved work capacity and gait function in patients with ALS who are dependent on assistive devices for ambulation. Repetitive rhythmic exercise-STAT should be evaluated further in larger studies to determine the stability of this improved function in relation to the rate of progression of the underlying pathologic state of ALS. A larger placebo control or crossover design clinical trial is needed to determine how well this preliminary effect may persist and potentially add to treatment effects over time.

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## Suppliers

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