Pulmonary Physical Therapy Techniques to Enhance Survival in Amyotrophic Lateral Sclerosis: A Systematic Review

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Background and Purpose: Respiratory insufficiency is the primary cause of morbidity and mortality in individuals with amyotrophic lateral sclerosis (ALS). Although mechanical interventions are effective in prolonging survival through respiratory support, pulmonary physical therapy interventions are being investigated. The purpose of this systematic review was to examine the effectiveness of pulmonary physical therapy interventions across the progressive stages of ALS.
Methods: Six databases were searched for articles from inception to December 2014 investigating pulmonary physical therapy interventions in the ALS population. The search strategy followed Cochrane Collaboration guidelines with replication per database. Effect sizes (ES) were calculated for primary outcome measures: forced vital capacity (FVC) and peak cough expiratory flow (PCEF).
Results: Seven studies met inclusion criteria. Four studies used control groups whereas the remainder used repeated measures. With the exception of diaphragmatic breathing, pulmonary physical therapy interventions were effective in improving multiple respiratory outcome measures in this population. Inspiratory muscle training (IMT) was shown to prolong respiratory muscle strength with a strong effect size (ES = 1.48) for FVC. In addition, mean length of survival increased by 12 months. Lung volume recruitment training (LVRT) strongly enhanced immediate cough efficacy with improved FVC (ES = 1.02) and PCEF (ES = 1.82). Manually assisted cough (MAC) only improved PCEF by a small amount (ES = 0.15, bulbar ALS; ES = 0.16, classical ALS groups).
Discussion and Conclusions: Specific pulmonary physical therapy interventions (IMT, LVRT, and MAC) have effectiveness in improving respiratory outcome measures and increasing survival. These should be routinely incorporated into the comprehensive management of individuals with ALS. More rigorous methodological investigations should be performed to replicate these findings.

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Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.jnpt.org).

The authors declare no conflict of interest.

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ISSN: 1557-0576/16/4003-0165
DOI: 10.1097/NPT.0000000000000136

Video abstract available with brief technique demonstration of IMT and LVRT (see Supplemental Digital Content 1, http://links.lww.com/JNPT/A136).

Key words: *amyotrophic lateral sclerosis, diaphragmatic breathing training, inspiratory muscle training, lung volume recruitment training, manual cough augmentation, pulmonary physical therapy, pulmonary physical therapy interventions*

(*JNPT* 2016;40: 165–175)

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease affecting both upper and lower motor neurons in the brain and spinal cord, and leads to a loss of voluntary muscle control. With disease progression, muscles of respiration are affected, leading to respiratory compromise and insufficiency. Respiratory insufficiency is primarily due to diaphragmatic weakness with significant decline in intercostal and axial muscle function. This involvement of respiratory musculature is the terminal event and primary source of morbidity and mortality among individuals with ALS.[1-3] In fact, inspiratory muscle strength is a prognostic indicator for survival.[3] Thus, the importance of approaches to manage respiratory decline and improve function in the ALS population is paramount in clinical care.[2]

The role of exercise in the ALS population is controversial. Studies have shown that high-intensity exercise is deleterious in the transgenic mouse model of ALS.[4] However, moderate-intensity aerobic exercise has been shown to be beneficial in both the animal and human models of ALS.[5-7] In addition, 3 investigations of submaximal resistive exercise for at least 3 months' duration demonstrated safety while significantly preserving muscle strength with less fatigue and participation limitations in the experimental groups.[6,8-10] The neuromuscular mechanism was thought to be prevention of disuse atrophy and more efficient motor unit recruitment.

Since there is growing evidence that submaximal resistance exercise in the ALS population is safe and efficacious in delaying the decline in skeletal muscle strength, and because respiratory insufficiency is the primary cause of mortality and morbidity in this population, maintaining respiratory muscle strength should be a key focus for the physical therapist. Respiratory muscle training and strengthening may in fact demonstrate similar safety and efficacy as well as serve as

a viable means to maintain function and slow respiratory declination.

Managing respiratory symptoms in ALS has been recognized as a practical means of improving patient functioning. Interventions to improve ventilation by enhancing both inspiration and expiration are advocated through the use of noninvasive mechanical devices such as bilevel positive airway pressure (Respironics) and cough assist devices (insufflation-exsufflation). In a literature review of treatment advances for respiratory failure in the ALS population, Pinto and deCarvalho[11] offer recommendations for when to implement these mechanical devices. More recently, pulmonary physical therapy interventions have been receiving increasing emphasis. These active rehabilitation approaches are being evaluated for their ability to enhance respiratory function immediately as well as over prolonged intervention duration. These approaches have also been used effectively in other progressive neuromuscular disease populations where weakness and fatigue are safety concerns.[12-14] The interventions include inspiratory muscle training (IMT), lung volume recruitment training (LVRT), manually assisted cough (MAC), and diaphragmatic breathing (DB) training. Although these approaches are mentioned in the review by Pinto and deCarvalho,[11] a systematic review of the literature following Cochrane guidelines with statistical meta-analysis has not been performed to date.

Rehabilitation Approaches for Improving Inspiration Efficiency

DB is the cornerstone of inspiration efficiency; the contraction of the diaphragm lengthens the thoracic cavity whereas intercoastal muscle contraction opens the ribs to increase lateral expansion, thus enhancing inspiration.[15] IMT is a long-duration intervention (months) used to strengthen the muscles of inhalation in an attempt to delay the progression of respiratory insufficiency. Although there are a variety of types of inspiratory muscle trainers, the threshold method of IMT uses a spring whose tension can be adjusted so resistive inspiration occurs with daily use. The exercise prescription for IMT is 10 minutes per day, 2 to 3 times a day and can be progressively increased. IMT also aids in reversing microatelectasis by allowing more air to enter into the lungs.[16-18] LVRT utilizes a series of breath-stacking maneuvers via a manual resuscitator (eg, Ambu bag) and cough-augmentation maneuvers (eg, abdominal thrusts) for immediate results. LVRT primarily aims to increase lung volume, decrease the work of breathing, and stimulate a forceful cough. It increases chest wall compliance and range of motion, aerates collapsed lung segments, reverses microatelectasis, and eliminates flow restrictions within the conducting airways.[19,20] MAC consists of cough augmentation via abdominal thrust with or without LVRT. MAC maneuvers aim to assist the patient in immediate removal of secretions from the airway by improving cough efficacy.[21-23]

Physical therapists recognize that planning care for individuals with ALS occurs along a continuum, which is dependent on disease stage and evaluation findings. Dal Bello-Haas and colleagues[24,25] have provided a rehabilitative framework for those with neurodegenerative diseases along with a case presentation. Because the continuum model has preventive and compensation intervention strategies identified and respiration is critical for survival, it is important to include respiratory interventions throughout the care continuum.

For physical therapists treating individuals with ALS who are engaged in evidence-based practice, it is important to incorporate pulmonary physical therapy interventions that are shown to be safe and effective in the comprehensive plan of care for this population. As with any intervention for neurologic clinical populations with progressive conditions, selection of the appropriate outcome measures is also important[26] The purpose of this systematic review was to examine the evidence for pulmonary physical therapy interventions in individuals with ALS across the progressive stages and determine its effectiveness.

METHODS

This systematic review utilized the Cochrane Collaboration recommendations with the process reported per the PRISMA statement.[27]

Study Inclusion and Exclusion Criteria

The inclusion criteria were as follows:

1. Experimental designs included randomized control trials, pilot studies, control trials, cross-over designs, and repeated-measures design trials.
2. Participants diagnosed with ALS according to the revised El Escorial criteria.
3. Investigated nonmechanical pulmonary interventions, including DB, IMT, LVRT, and MAC techniques.
4. Outcome measures included but not limited to standardized measures of respiratory function (eg, FVC, forced expiratory volume in the first second of expiration, total lung capacity, vital capacity, and PCEF). Outcome measures included were those that physical therapists routinely refer to for clinical decision making of pulmonary interventions.
5. English language full-text articles.

Exclusion criteria were as follows:

1. Participants with undefined motor neuron disease and not ALS or ALS combined with another neurologic or respiratory comorbidity
2. Pulmonary interventions that evaluated only mechanical devices
3. Pulmonary physical therapy interventions combined with respiratory medications

Search Methods for Identification of Studies

The following 6 databases were searched from inception to December 2014: The Cochrane Library, Ovid MEDLINE, PubMED, Health and Psychosocial Instruments, AMED, and EBSCO CINAHL.

Please see Appendix I (Supplemental Digital Content 2, http://links.lww.com/JNPT/A137) for MEDLINE strategy and associated search terms. This search strategy was replicated with all electronic databases. In addition, we searched for ongoing trials in the World Health Organization International Clinical Trials Registry Platform. Finally, we hand searched reference lists for additional articles.

Data Collection and Analysis

Selection of Studies

Both review authors screened titles, abstracts, and descriptors of identified studies for possible inclusion in this review. From the full-text of each article, both review authors assessed whether or not inclusion and exclusion criteria were met. Any disagreement was resolved via discussion. Studies meeting established guidelines were reviewed by both authors for analysis.

Data Extraction and Management

Each eligible article was assessed using a modified Critical Review Form for Quantitative Studies while incorporating a predetermined data extraction procedure.[28,29] Data extracted included sample size, study design, experimental, and control outcomes for each testing session. For a complete listing, please see the table of study characteristics (Table 1).

The primary outcome measures extracted for this systematic review included peak cough expiratory flow (PCEF) and forced vital capacity (FVC). Secondary outcome measures were ALSFRS-R (ALS Functional Rating Scale Revised), which identifies the impact of the disease on participation and survival time to determine whether an intervention impacted survival.

Assessment of Risk of Bias in Included Studies

Both authors independently assessed risk of bias for each included study using the Cochrane Collaboration Risk of Bias Tool.[30] Any disagreement was resolved through discussion. The domains assessed were selection, performance, detection, attrition, reporting, and other bias.

Measures of Treatment Effect

Study data extracted were compiled and summarized (Appendix II). If reviewed studies provided mean and standard deviation values for both control and experimental groups at baseline and postintervention, within-group and between-group effect sizes were calculated using Cohen's *d* formula (*d*).[31] If a reviewed study only provided between-group mean difference values with accompanying standard deviation, then these values were used to determine between-group effect sizes. For studies that used repeated-measured designs, only within-group effect sizes were calculated. If only median values were reported, no effect sizes could be calculated.

Dealing With Missing Data

We reported levels of attrition and assessed impact of missing data on conclusions.

Overall Evidence Quality Assessment

Using the Cochrane GRADE system, we assessed the evidence as high, moderate, low, or very low quality on the basis of the level of evidence of the combined studies and consideration of the biases in the identified domains.[30]

RESULTS

To examine the effectiveness of pulmonary physical therapy (PT) interventions on individuals with ALS, we first report the results of our search with respect to design and outcome measures. Next, we detail the specific pulmonary PT interventions, followed by our analysis of effect size on primary and secondary outcome measures. Finally, risk of bias is reported.

Results of the Search

Our initial search resulted in 1233 eligible articles, with 266 records remaining after duplicate removal. As of December 2014, no systematic reviews regarding the effects of pulmonary physical therapy interventions for individuals with ALS were identified. Refer to the flow sheet (Figure 1) for the systematic review article identification process. Nine studies remained for qualitative synthesis. However, 2 studies were removed because we were unable to obtain full-text English language versions. Ultimately, 7 studies met inclusion criteria for this systematic review.

Study Design

The research designs were varied. Four studies used control groups with multiple designs: randomized control trial,[32] experimental-historical control trial,[33] randomized cross-over trial,[34] and repeated-measures cross-over design.[35] The remainder were studies with repeated-measures designs.[36-38] The 7 studies were conducted in the following countries: Australia, Canada, Portugal, Spain, the United Kingdom, and the United States of America. Publication dates were recent: 2003 to 2013. For further information, refer to study characteristics and study interventions and results (Table 1 and Appendix II).

All 7 studies included individuals with ALS (n = 144) throughout varying stages and subgroups (bulbar, nonbulbar/classical). One study included subjects with pseudobulbar palsy and primary lateral sclerosis.[32] Four pulmonary physical therapy interventions were investigated: IMT (n = 3), LVRT (n = 1), MAC (n = 2), and DB training (n = 1). Duration of interventions varied tremendously: 1 day to 32 months. When comparing treatment outcomes, 6 studies reported FVC, 3 reported PCEF, and 3 reported change in ALSFRS-R. Other less frequently reported measures included vital capacity (VC), maximal inspiratory pressure/maximal expiratory pressure, total lung capacity, maximal ventilator volume, sniff nasal inspiratory pressure, quality of life, total survival rates, fatigue, phrenic nerve amplitude, and cough volumes (Table 1).

Specific Manual Pulmonary Interventions

Inspiratory Muscle Training

In the double-blind randomized clinical trial (RCT) by Cheah and colleagues,[32] subjects underwent a 12-week IMT program with an 8-week retention test. Subjects had a mean (standard deviation) FVC predicted value of 85.8 (±20.2). Postintervention all respiratory outcomes demonstrated improvement for the experiment versus control group. FVC, total lung capacity, and maximal inspiratory pressure highlighted improved inspiratory muscle strength (Appendix II). However, these improvements were not maintained at 8-week retention. No group difference was demonstrated at either assessment for ALSFRS-R.

A study by Pinto and colleagues[34] examined IMT using a cross-over design, running parallel randomized control and

Table 1. Study Characteristics

Author	Experiment Design	Participants, N	Mean Age (SD)	Gender Composition	Type of ALS	ALS Disease Markers Baseline Experiment Mean (SD)	ALS Disease Markers Baseline Control Mean (SD)	Intervention	Outcome Measures
Pinto and deCarvalho[33]	Follow-up comparison to historical control	Total N = 34 Experiment group N = 18 Control group N = historical control 16	57 (8.9)	14 females; 20 males	7 bulbar 27 classical	ALSFRS: 34.3 (2.4) R of ALSFRS-R: 11.67 (0.49) FVC (% predicted): 101.9 (14.8) Phrenic nerve amplitude (mV): 0.8 (0.3) Total survival time (mo): 36.99 (13.1)	ALSFRS: 33.8 (3.3) R of ALSFRS-R: 11.81 (0.54) FVC (% predicted): 95.7 (12.6) Phrenic nerve amplitude (mV): 0.63 (0.16) Total survival (mo): 24.06 (11)	Intervention duration: from 8 to 32 mo E: Active IMT training protocol: twice/day for 8 mo Each subject practiced for 10 min, with intensity set at 30%-40% MIP, twice/day. Subjects engaged in the Pinto et al[34] IMT protocol for as long as possible C: Historical control, no intervention received	ALSFRS-R, R of ALSFRS-R, FVC (% predicted), Total survival time (mo) Phrenic nerve amplitude (mV)
Pinto et al[34]	Randomized cross-over design	Total N = 26 Experiment group N = 13 Control group N = 13	57 (8.9)	8 females; 18 males	4 bulbar 22 classical	Disease duration: 11.5 (5.3) ALSFRS: 34.39 (3.64) ALSFRS-R score: 11.85 (0.38) FVC sit: 96.86 (21.4) FVC lay: 90.39 (21.84) PCEF sit: 84.16 (24.9) PCEF lay: 74.03 (31.74) MIP sit: 70.3 (27.7) MIP lay: 63.69 (26.4) SnP sit: 74.15 (24.4) SnP lay: 73.23 (25.76) MVV sit: 76.05 (31.8) MVV lay: 64.75 (33.75) Phrenic amplitude (mV): 0.86 (0.33)	Disease duration: 12.6 (6.6) ALSFRS: 33.5 (3.8) ALSFRS-R score: 11.77 (0.44) FVC sit: 85.99 (15.47) FVC lay: 83.99 (21.16) PCEF sit: 89.61 (24.76) PCEF lay: 79.8 (23.39) MIP sit: 78.46 (25.86) MIP lay: 72.54 (27.15) SnP sit: 84.54 (25.12) SnP lay: 89.85 (27.57) MVV sit: 78.55 (18.58) MVV lay: 64.76 (17.36) Phrenic amplitude (mV): 0.79 (0.24)	Intervention duration: 8 mo E: Active IMT training protocol: twice/day for 8 mo Each subject practiced for 10 min, with intensity set at 30%-40% MIP, twice/day C: Placebo IMT training protocol for first 4 mo, then progress to active IMT training protocol for last 4 mo During placebo period, subjects would breathe into the respiratory device at the lowest possible load for the same set parameters	ALSFRS R of ALSFRS-R FVC PCEF (L/min) MIP/MEP MVV SnP Phrenic nerve amplitude (mV) Fatigue QofL
Cleary et al[35]	Repeated-measures, cross-over design	Total N = 29 Experiment group N = 29 Control group N = N/A	65.4 (11.5)	13 females; 16 males	6 bulbar 22 classical 1 respiratory	Median score on ALSFRS-R was 29.3, ranging from 14 to 41 out of a possible 48 FVC ranges from 23% to 93% on predicted normal values	N/A	Intervention duration: 2 d E: LVR treatment: 5 maximal insufflations, with 2 trials of augmented cough C: Same as intervention, subjects served as their own control.	FVC SnP PCEF
Senent et al[38]	Repeated-measures design	Total N = 16 Experiment group N = 16 Control group N = N/A	63	4 females; 12 males	Classical ALS Bulbar ALS	Bulbar Norris bulbar score: 5(4-13) ALSFRS-R: 13 (12-20)	N/A	Intervention duration: 1 d E: 3 MAC techniques: (1) Unassisted cough (2) Coached unassisted cough (3) Cough with abdominal thrust. Instrumental techniques:	PCEF

(continues)

Table 1. Study Characteristics (*Continued*)

								(1) Abdominal thrust with air stacking (2) Abdominal thrusts and BiPAP (3) Abdominal thrusts plus IPAP 30 cm H_2O (4) Cough assist via in/exsuffalator All maneuvers performed on the same day with 10-15 min interval breaks between segments 1-h rest between manual vs instrumental C: Same as intervention, subjects served as their own control.	
Cheah et al[32]	Double blind RCT	Total N = 19 Experiment group N = 9 Control group N = 10	E 54.2 (9.8); C 53.4 (9.5)	7 females; 12 males	15 classical ALS 1 pseudobulbar palsy 3 primary lateral sclerosis	Disease duration (mo): 29.89 (15.7) ALSFRS-R: 38.2 (6.5) FVC: 85.8 (20.2) VC % predicted mean: 83.8 (18.1) SnP % predicted mean: 78.5 (35.6) MIP % predicted mean: 81.3 (35.2)	Disease duration (mo): 34.69 (33.8) ALSFRS-R: 38.99 (2.7) FVC: 83.69 (16.7) VC % predicted mean: 80.39 (15.2) SnP % predicted mean: 78.0 (99.3) MIP % predicted mean: 70.69 (29.0)	Intervention duration: 12 wk E: Group introduction: 1-4 visits. Home instruction: IMT for 10 min, 3 times per day, 7 d/wk for 12 wk. Intensity initially set to 15% of SnP, progressing to 30%-45%-60% Also training diaries were used C: Sham IMT treatment (spring-loaded valve removed, no resistance) Home instruction: 10 min, 3 times per day, 7 d/wk for 12 wk	ALSFRS-R Vital capacity FVC MIP Total lung capacity SnP 6MWT
Nardin et al[36]	Repeated-measures pilot study	Total N = 8 Experiment group N = 8 Control group N = N/A	63.3 Range 37-78	1 female; 7 males	Definite or probable ALS with respiratory involvement	Definite or probable ALS and respiratory involvement defined as an FVC between 50% and 80% of predicted normal values	N/A	Intervention duration: 3 sessions E: Patients instructed on diaphragmatic breathing Inhalation count of 3, exhalation count of 5 for 5 cycles Progress to inhale count of 3, exhale count of 10 for 5 cycles. Progress to inhale count of 3, exhale count of 15 for 5 cycles Repeated for 10 min Home instruction was 5×10 min/d. Practice logs provided C: Same as intervention, subjects served as their own control	FVC
Mustfa et al[37]	Repeated-measures design	Total N = 57 Experiment group N = 47 Healthy control N = 10 Total participants across studies N = 191 Total experiment group N = 142 Total control group N = 49 If applicable based off study design	Not listed	15 females; 32 males	21 bulbar 26 nonbulbar	Not formally described, however Norris bulbar score ≤ to 35 Bulbar: PCEF (L/min): 178 (61) Cough volume (L/min): 0.98 (0.3) Nonbulbar: PCEF (L/min): 217 (84) Cough volume (L/min): 1.16 (0.5)	N/A	Intervention duration: 1 d E: Subjects coughed into a tight-fitting full-face mask. 5 coughs performed: (1) Maximal unaided cough (2) Maximal aided cough with PT provided abdominal thrust (3) Exsufflation only on cough assist (4) Insufflation only on cough assist (5) Combined in/exsufflation on cough assist Each cough performed in random order to avoid bias C: Same as intervention, 10 healthy controls used to examine difference	PCEF

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; BiPAP, bilevel positive airway pressure; C, control group; DB, diaphragmatic breathing; E, experiment group; FVC, forced vital capacity; IMT, inspiratory muscle training; LVRT, lung volume recruitment training; MAC, manually assisted cough; MIP, maximal inspiratory pressure; MVV, maximal voluntary ventilation; 6MWT, 6-minute walk test; #N, number of subjects; PCEF, peak cough expiratory flow; QofL, quality of life; R of ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale (Revised)—respiratory subset; RCT, randomized clinical trial; SD, standard deviation; SnP, sniff nasal pressure; VC, vital capacity.

Total Survival Rates, Fatigue, Phrenic Nerve Amplitude and Cough Volumes

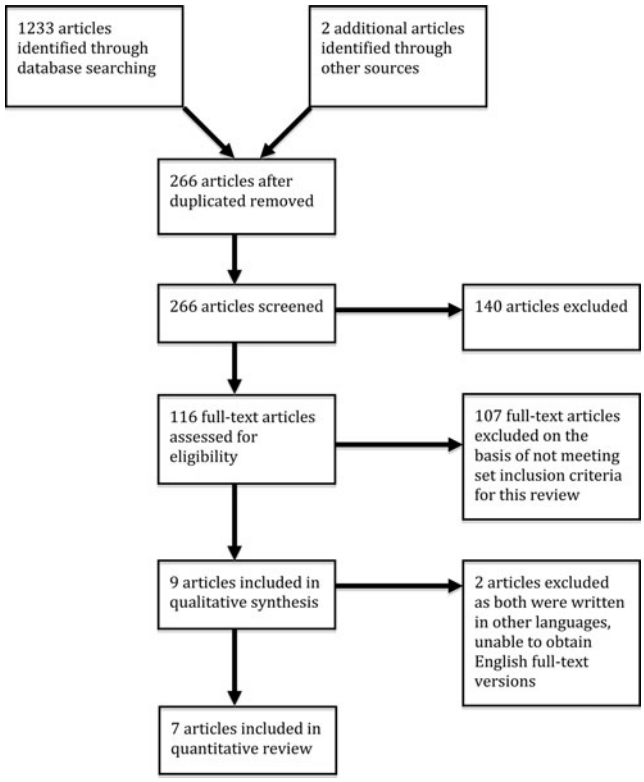

Figure 1. Flow sheet.

experiment groups the first 4 months. Subjects had a mean FVC value between 85.99 and 96.86. During the next 4 months, both groups underwent the same IMT intervention. Many respiratory outcome measures were tested in seated and supine positions (Appendix II). At the 4-month outcome assessment, FVC values were higher for the experiment versus control group in both positions. As expected FVC values in sitting positions were greater than in supine positions. In addition, ALSFRS-R values demonstrated a slower decline for experiment over the control group.

At the 8-month assessment, where both groups were receiving IMT, FVC in sitting was significantly higher for the original experiment group. All other respiratory measures and ALSFRS-R tended to decline less for the IMT group over the 8-month period but were not statistically significant.

In their follow-up study, Pinto and deCarvalho[33] continued to assess IMT effectiveness in surviving subjects who maintained the ability to perform the intervention. The original experimental group was compared with an historical control group of individuals with ALS who received no intervention. They recorded subject IMT duration (eg, 8, 12, 18, 24, and 32 months). Survival statistics were calculated. IMT and FVC were significant prognostic factors (Appendix II). In addition, male gender, 0.7 mV or less phrenic nerve amplitude, and not performing IMT were found to increase mortality risk between 2.3 and 3-fold (Appendix II). Most importantly, individuals with ALS who participated in IMT survived significantly longer than those in the historical control group by a mean of 12 months (Table 1).

Lung Volume Recruitment Training

In the repeated-measures cross-over study by Cleary and colleagues,[35] subjects with ALS were counterbalanced to receive either a 1-day trial of LVRT or no intervention (control). Then on a following day (2-7 days after) the individuals switched groups. Each LVRT trial consisted of 5 breaths with manual resuscitator and 2 augmented coughs. Both groups were assessed at 15 and 30 minutes postintervention or control condition for pulmonary function and cough efficacy. All subjects were using LVRT for a mean of 4.8 months. Their FVC ranged from 23% to 93% predicted normal values. Compared with baseline values, LVRT significantly increased FVC and PCEF values immediately postintervention. At 30 minutes the higher PCEF values were maintained. No statistically significant differences were seen for sniff nasal pressure.

Manual Cough Assist Technique

In Mustfa and colleagues[37] repeated-measures study, subjects with ALS (separated into bulbar and nonbulbar groups) and healthy controls underwent a 1-day trial of 5 randomly assigned assisted cough techniques: maximal unaided cough, MAC via abdominal thrust, and 3 mechanically enhanced cough techniques with insufflation and/or exsufflation. Healthy control results were reported to demonstrate effectiveness of mechanical techniques. All participants with ALS had reported mean baseline PCEFs, which were less than 225 L/min (bulbar: 178 L; nonbulbar: 217 L) and reduced predicted VCs (bulbar: 54%; nonbulbar: 68%). This PCEF is near the 160 L/min minimum threshold for effective secretion removal and below the 270 L/min recommended threshold for implementation of assisted cough techniques.[22,39] As expected, mechanical devices were shown to be significantly more effective than MAC technique in the ALS population. Exsufflation improved PCEF in both bulbar (26%) and nonbulbar groups (28%). However, the MAC technique did significantly improve PCEF in both groups from their baseline measures. Mean PCEF in the bulbar group rose to 197 L/min and in the nonbulbar group to 244 L/min. Authors noted the greatest improvements in cough efficacy, regardless of intervention, were seen in those individuals presenting with the weakest coughs.

Similarly, in a repeated-measures study by Senent and colleagues,[38] subjects with ALS underwent a 1-day trial of 7 manual or mechanical techniques to evaluate cough effectiveness. Included subjects had an unassisted PCEF value of less than or equal to 270 L/min or more and were on home mechanical ventilation for 2 months or more. Four cough techniques were delivered in this order (unassisted cough, coached unassisted cough, cough with abdominal thrust (MAC), breath stacking via manual resuscitator with abdominal thrust—MAC+: similar to LVRT technique) and then followed by 3 sequentially delivered mechanically enhanced cough techniques (abdominal thrust after end-expiratory lung volume via bilevel positive airway pressure, abdominal thrust after end-expiratory lung volume via inspiratory positive airway pressure, and mechanically assisted cough via insufflation-exsufflation). The first 3 cough interventions were significantly less effective than the last 4 techniques. The MAC+ technique had a median value PCEF of 284 L/min and was not significantly different from the other 3 mechanically assisted cough

techniques. In addition, no significant difference for MAC+ technique was seen between bulbar and nonbulbar groups. Use of coached unassisted cough and coached cough with abdominal thrust raised PCEF, however not significantly and never more than 270 L/min. Finally, subjects' preferred method of cough augmentation was not always the mechanical devices.

Diaphragmatic Breathing

In a repeated-measures study by Nardin and colleagues,[36] 8 subjects with ALS underwent a 12-week training of yoga-style DB. Baseline predicted FVC values ranged from 51% to 89%. No significant improvements were noted for FVC, standard progressive hypercapneic ventilatory response, respiratory magnetometry, or quality of life. Subjects reported difficulty mastering the technique. However, in 3 of the 4 subjects able to master the technique, a slower rate of respiratory decline was observed.

Effect Size

Between-Group Effect

FVC & PCEF. Because of experimental designs, only 3 studies could be used to determine between-group effect sizes for FVC or PCEF (Tables 2 and 3, Figure 2).[32,34,35] Overall, Cleary and colleagues' LVRT intervention demonstrated high clinical utility to improve cough efficacy immediately for removal of secretions. FVC results demonstrated a large immediate positive effect at 15 minutes ($d = 1.022$) and a negligible negative effect at 30 minutes ($d = -0.123$). Together, these support the immediate effectiveness in enhancing lung volume for the LVRT intervention. After LVRT, PCEF values demonstrated a large effect at 15 and 30 minutes postintervention ($d = 1.82$, $d = 1.46$, respectively), suggesting an extended treatment duration for cough expiratory flow. As expected, effect sizes at 15 minutes were greater than at 30 minutes.

Both Pinto and colleagues'[34] and Cheah and colleagues'[32] long duration (4 months and 12 weeks, respectively) IMT intervention yielded large effect sizes postintervention for FVC. As expected the effect size seated ($d = 1.48$) was greater than supine ($d = 0.7588$) in the study by Pinto and colleagues.[34] The effect size in the study by Cheah and colleagues[32] was similarly strong ($d = 1.57$). These results suggest IMT has high clinical utility to improve the strength of inspiratory muscles and prevent respiratory decline.[32]

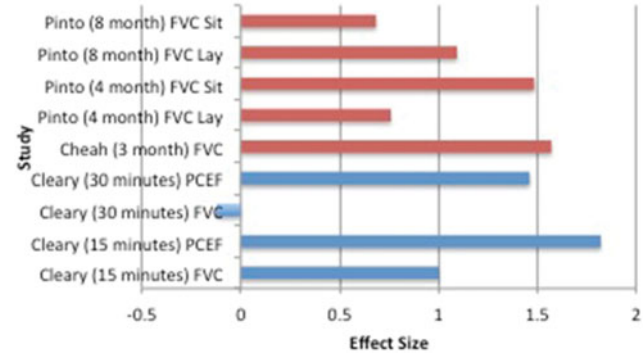

Figure 2. Between-group effect size for PCEF and FVC. Red indicates inspiratory muscle training whereas blue indicates lung volume recruitment training. Abbreviations: FVC, forced vital capacity; PCEF, peak cough expiratory flow.

ALSFRS-R. Only 2 investigations reported changes to ALSFRS-R (Table 4 and Figure 3). Pinto and colleagues[34] demonstrated a moderate positive effect at 4 months postintervention ($d = 0.5814$). However, Cheah and colleagues[32] demonstrated a negligible positive effect postintervention ($d = 0.05$). These results suggest low clinical significance for IMT to slow the participation decline in individuals with ALS.

Within-Group Effects

PCEF. The remainder of the investigations did not utilize control groups; therefore, only within-group effect sizes

Table 2. Effect Sizes for Forced Vital Capacity

	FVC							
	Initial Mean (SD)		Post Mean (SD)		Within Effect Size		Between-Group Mean Difference (SD_{pooled})	Between-Group Effect Size
Author	Experiment	Control	Experiment	Control	Experiment	Control		
Pinto and deCarvalho[33]	101.9 (14.8)	95.7 (12.6)	NR	NR	NR	NR	NR	NR
Pinto et al,[34] 4 mo sit	96.86 (21.4)	85.99 (15.47)	NR	NR	NR	NR	10.86 (7.324)	1.48279
Pinto et al,[34] 4 mo lay	90.39 (21.84)	83.99 (21.16)	NR	NR	NR	NR	6.4 (8.434)	0.7588
Cleary et al,[35] 15 min	2.23 (0.93)	2.11 (0.86)	2.30 (0.92)	2.11 (0.83)	0.03781	0	0.07	1.002
Cleary et al,[35] 30 min	2.23 (0.93)	2.11 (0.86)	2.25 (0.95)	2.14 (0.82)	0.01063	0.01784	-0.01	-0.123
Cheah et al,[32]	85.8 (20.2)	83.6 (16.7)	NR	NR	NR	NR	4.59 (3.02)	1.57
Nardin et al,[36] 6 wk	69.5 (14.56)	NA	65.88 (22.25)	NA	−0.1220	NA	NA	NA
Nardin et al,[36] 12 wk	69.5 (14.56)	NA	64.00 (20.16)	NA	−0.1545	NA	NA	NA

Abbreviations: FVC, forced vital capacity; NA, not applicable, primarily based off study design; NR, not reported; SD, standard deviation; SD_{pooled}, pooled group standard deviation.

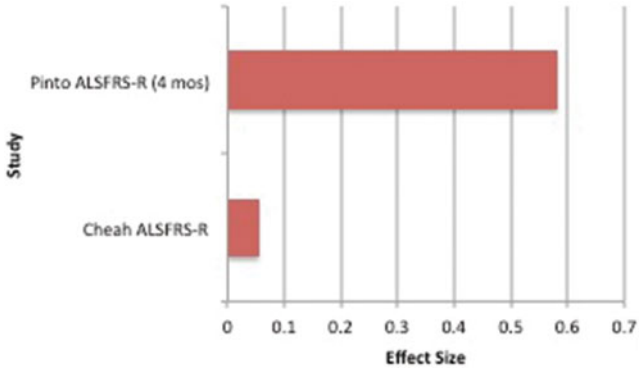

Figure 3. Between-group effect size for ALSFRS-R. Red indicates inspiratory muscle training. Abbreviation: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale (Revised).

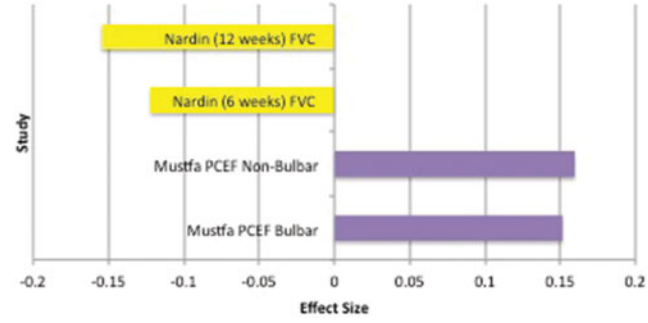

Figure 4. Within-group effect size for PCEF and FVC. Yellow indicates diaphragmatic breathing whereas purple indicates manually assisted cough techniques. Abbreviations: FVC, forced vital capacity; PCEF, peak cough expiratory flow.

were calculated (Table 3). Within-group effect size for immediate changes in PCEF was shown to be positive (Figure 4). The MAC techniques used by Mustfa and colleagues[37] demonstrated small positive effects postintervention for individuals with ALS in both bulbar and nonbulbar groups ($d = 0.306$, $d = 0.323$, respectively). This investigation has moderate clinical utility to show change immediately.

FVC. Given the progressive nature of ALS, it was expected that long-duration interventions would yield negative within-group effect sizes (Table 2). This was the case for FVC with the DB intervention, suggesting low clinical utility. Figure 4 demonstrates the negative effect for the DB intervention used by Nardin and colleagues[36] at 6 and 12 weeks ($d = -0.237$, $d = -0.305$, respectively). This may suggest disease progression or treatment ineffectiveness. Without a control group the impact of each cannot be discerned.

Risk of Bias in Included Studies

Refer to Appendix III for individual study risk of bias assessment, and Figure 5 for risk of bias summary. Because of the rapid degenerative nature of ALS and the ethics surrounding withholding potentially beneficial treatments, most studies allocated all participants to receive the interventions investigated. This increased the bias across all domains, making the overall Cochrane grade low.

Two studies randomly assigned subjects to receive an intervention. Allocation bias was low across all studies. With the exception of Cheah and colleagues'[32] study and the first

Table 3. Effect Sizes for Peak Cough Expiratory Flow

	PCEF							
	Initial Mean (SD)		Post Mean (SD)		Within Effect Size		Between-Group Mean Difference (SD_{pooled})	Between-Group Effect Size
Author	Experiment	Control	Experiment	Control	Experiment	Control		
Cleary et al,[35] 15 min	251.35 (118.55)	263.08 (130.24)	305.00 (140.70)	255.19 (120.90)	0.20194	−0.0313	61.54	1.82
Cleary et al,[35] 30 min	251.35 (118.55)	263.08 (130.24)	295.38 (122.99)	259.62 (122.25)	0.17930	−0.0136	47.49	1.46
Senent et al[38]	Total: 84 (35-118)	NA	Coached cough: 79 (36-142)	NA	NR	NA	NA	NA
Results reported in median (25th-75th percentile)			Coach + thrust: 104 (80-140)					
			Thrust + breath stacking: 284 (146-353)					
Mustfa et al[37]	Bulbar Unassisted: 178 (61)	NA	Bulbar Manual assist: 197 (63)	NA	Bulbar 0.15143	NA	NA	NA
	Nonbulbar Unassisted: 217 (84)		Nonbulbar Manual assist: 244 (83)		Nonbulbar 0.15960			

Abbreviations: NA, not applicable, primarily based off study design; NR, not reported; PCEF, peak cough expiratory flow; SD, standard deviation; SD_{pooled}, pooled group standard deviation.

Table 4. Effect Sizes for ALSFRS-R

	ALSFRS-R							
	Initial Mean (SD)		Post Mean (SD)		Within Effect Size		Between-Group Mean Difference (SD_{pooled})	Between-Group Effect Size
Author	Experiment	Control	Experiment	Control	Experiment	Control		
Pinto and deCarvalho[33]	34.3 (2.4)	33.8 (3.3)	NR	NR	NR	NR	NR	NR
Pinto et al,[34] 4 mo	34.39 (3.64)	33.5 (3.8)	NR	NR	NR	NR	0.846 (1.455)	0.581
Cheah et al[32]	38.29 (6.5)	38.99 (2.7)	NR	NR	NR	NR	0.049 (0.73)	0.054

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale (Revised); NA, not applicable, primarily based off study design; NR, not reported; SD, standard deviation; SD_{pooled}, pooled group standard deviation.

Figure 5. Risk of bias summary. Green indicates low risk of bias, yellow indicates unclear risk of bias, and red indicates high risk of bias.

half of Pinto and colleagues'[34] crossover study, subjects were aware of the interventions received. Only 3 studies mentioned blinded assessors. Four studies reported low attrition and reporting biases. Only one study demonstrated low overall bias with the exception of a reporting bias.[32]

Three studies presented unclear bias. The order of MAC interventions was not randomized across subjects in Senent and colleagues'[38] investigation. MAC interventions while randomized were performed all on the same day in Mustfa and colleagues'[37] investigation. In both studies, the potential for summation effect was high. Finally, some participants in Cleary and colleagues'[35] LVRT investigation were in his dissertation study, thus making the subject pool tainted.

DISCUSSION

This is the first systematic review evaluating the effectiveness of pulmonary physical therapy interventions in individuals with ALS. Only 7 articles met inclusion criteria. The studies varied in design, progression of the disease, outcome measures reported, intervention type, and duration. The most often reported outcome measures were FVC and PCEF.

The strength of the evidence supports using IMT for long-term benefit and LVRT for short-term benefit in individuals with ALS. Because individuals with ALS succumb to respiratory insufficiency, it is imperative to identify and subsequently intervene with pulmonary physical therapy interventions that may prolong life by enhancing respiratory function. Prolonged IMT use in individuals with ALS was a factor that enhanced survival time when compared with historical controls. These individuals performed IMT for at least 8 months in duration, suggesting IMT be initiated early when respiratory function is minimally compromised and maintained for as long as feasible.

Strengthening of the respiratory musculature through IMT in this population may be even more powerful when juxtaposed with the moderate-intensity extremity strengthening and aerobic exercise studies that measured FVC. Lui and Byl's[6] systematic review of moderate-intensity exercise on function in early-stage ALS showed an FVC effect size of 1.2. Both Pinto and colleagues'[34] and Cheah and colleagues'[32] effect sizes for IMT were larger ($d = 1.48$, $d = 1.57$, respectively), supporting the principles of exercise training—overload principle, specificity of training, individual differences, reversible

nature of training, and progression of exercise.[40] If one wishes to strengthen respiration than resistive, exercise to the respiratory musculature is needed.

The evidence further suggests that LVRT is most beneficial for immediate enhancement of cough efficacy and removal of secretions. Timing this intervention to occur postmeal ingestion and both before and after sleep may be beneficial to prevent aspiration of food particles and/or secretions. This technique is most effective in individuals with minimal to moderate respiratory compromise as measured by FVC (range 23%-93% predicted normal) and PCEF values less than 270 L/min, which is the recommended threshold for initiating assisted cough techniques.

Although MAC techniques are similar to LVRT in their targeted goal of improving cough efficacy, the evidence demonstrates low-moderate benefit for this intervention alone. In the 2 studies where this technique was performed, augmented cough through abdominal thrust maneuvers alone did not elevate the PCEF value more than 270 L/min.[37,38] However, breath stacking with augmented cough did and was the only MAC technique to do so. So the evidence suggests that to improve cough efficacy and remove secretions, increasing inhalation via breath stacking or manual resuscitator followed by abdominal thrust maneuvers should be performed.

The evidence from the single article on long-term DB indicates no benefit of this intervention on improving/maintaining respiratory function.[36] As reported in the literature, this specific DB technique was difficult to master. However, if mastered, the potential to maintain lung volumes in those with ALS may occur. Because of disease progression and respiratory decline, effective evaluation of this technique would require the inclusion of a control group, which is not ethical. However, similar to Pinto and deCarvalho's[33] historical control comparison, a similar design may be utilized for this long-duration intervention.

Potential Biases in the Review Process

When examining the level of evidence, the studies have high bias. Randomized controlled trials are lacking in this population and not ethical for long-duration interventions. Hence, only one study used a RCT, with the remainder using less rigorous experimental designs when including control groups (ie, randomized cross-over, and comparison to historical control). Repeated-measures designs were utilized when investigating interventions, which yielded immediate results. However, these interventions are most amenable to RCT design if subjects are matched appropriately.

Small sample sizes were utilized. This may be due to the low prevalence of ALS (3.9 cases/100 000 persons in US general population),[41] lack of research interest in nonmechanical pulmonary methods, or strict inclusion criteria (ie, minimal respiratory involvement) for study eligibility. Regardless, the small sample sizes may have skewed results and support the need for larger multicenter clinical trials to further examine the efficacy of these interventions. Furthermore, within this systematic review of pulmonary physical therapy interventions, participant engagement duration and data collection time points varied. Finally, data presentation varied widely across studies (eg, mean, median, within-group mean difference, and between-group mean difference), which made comparison of each intervention difficult.

CONCLUSIONS

Even though there is limited research, specific pulmonary physical therapy interventions including IMT, LVRT, and MAC have at least moderate strength for effectiveness in improving respiratory outcome measures, participation level, and increasing survival. The type and effectiveness of the pulmonary physical therapy intervention used may ultimately depend on the individual's disease progression and comfort. More rigorous methodological interventions should be performed to replicate and expand upon these findings.

Implications for Physical Therapy Practice and Research

The existing evidence for pulmonary physical therapy techniques in individuals with ALS supports the use of initiating IMT in the early stage of the disease with continued use for as long as feasible. For immediate removal of secretions through enhancing cough efficiency, it is important that LVRT be taught to individuals with ALS and their caregivers as soon as possible.

For those pulmonary interventions that have immediate effectiveness such as LVRT or MAC, randomized controlled trials with matching for respiratory function should be initiated controlling for stage of disease and pulmonary status. Because it is unethical to deny a beneficial treatment, the longer duration IMT should utilize a randomized delayed start experimental design with similar matching.

ACKNOWLEDGMENT

The authors acknowledge the reviewers for their constructive feedback, which enhanced the scholarship of the document.

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