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Respiratory physiotherapy in patients with Amyotrophic Lateral Sclerosis. A systematic review

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Abstract

Introduction: Amyotrophic lateral sclerosis is a central nervous system disease with a progressive degeneration of superior and inferior motor neurons, causing several complications, specially respiratory problems. Respiratory physiotherapy has a great importance in this disease, since it can improve considerably the pulmonary function and gases changes, increasing the air volumes and decreasing the respiratory work, facilitating then the elimination of bronchial secretions. Thus, the aim of this study is to review the scientific literature in the last 5 years about the physiotherapy in ALS patients.

Development: A systematic review was carried out, searching in PubMed and Web of Science with the terms "amyotrophic lateral sclerosis" y "respiratory therapy". 217 results were obtained, and after the inclusion and exclusion criteria 19 studies were selected. All works analyzed carried out different interventions in respiratory physiotherapy such as VNI, phrenic stimulation, *Cough-Assist* or exercise therapy.

Conclusions: Respiratory physiotherapy seems to be effective for patients with ALS, except from phrenic stimulation.

Keywords: *Amyotrophic lateral sclerosis, Respiratory therapy, physiotherapy*.

Introduction

Amyotrophic lateral sclerosis (ALS) is a disease of the central nervous system (CNS) characterized by progressive degeneration of upper motor neurons (UMN) and lower motor neurons (LMN), resulting in weakness of limb, thoracic, abdominal and bulbar muscles[1]. It causes hyperreflexia, spasticity, muscle fasciculations, muscle atrophy, weakness and ultimately progresses to functional quadriplegia[2].

ALS is characterized by weakness of the respiratory muscles and a progressive decrease in lung function[3]. Impairment of the respiratory muscles, including the diaphragm, accessory muscles of respiration and bulbar muscles, leads to death through mechanisms of aspiration, decreased airway clearance due to ineffective coughing, pulmonary infections and chronic hypercapnic respiratory failure[4]. The disease usually leads to death within 3 to 5 years of diagnosis, the most common cause being respiratory failure[5].

It is usually sporadic with an incidence of 2 to 3 persons/year per 100,000 in European populations6 and a prevalence of approximately 3 to 5 per 100,0004.

It usually begins in the extremities, but in about one-third of cases it begins in the bulbar muscles responsible for speech and swallowing. Most cases of ALS are idiopathic, but approximately 10% of cases are due to genetic and autosomal dominant inheritance[2]. Survival is reduced by bulbar dysfunction, frontotemporal dementia, advanced age, rapid progression, repeated expansion of the C9orf72 gene, diagnostic delay, and low forced vital capacity (FVC)[3].

Respiratory physiotherapy plays an essential role in this pathology. The goals of respiratory physiotherapy are to improve lung function, raise air volumes, boost gas exchange, lower respiratory work, and make it easier for mucus to leave the tracheobronchial tree. To achieve these objectives, various manual and instrumental techniques are available[7]. The aim of this study is to analyze the scientific literature of the last five years on respiratory physiotherapy in ALS patients.

Materials and methods

To review the scientific evidence on this topic, a search of scientific articles was performed in PubMed and Web of Science during the months of January and February 2020, using the search terms "amyotrophic lateral sclerosis" and "respiratory therapy.". In addition, in order to limit the results obtained, selection criteria were established. As inclusion criteria, only those articles between 2015 and 2020 that were written in English were accepted, and as exclusion criteria, literature reviews and those that did not fit the objective were eliminated. The search equations obtained in each database are detailed in Table 1.

Table 1. Development of the search

Databases	Search equation	Results (with filters)	Discarded	Discarded
Pubmed	("Amyotrophic Lateral Sclerosis"[Mesh]) AND "Respiratory Therapy"[Mesh	508 (118)	14 reviews 86 do not fit the subject	18
Web of Science	Tema: (amyotrophic lateral sclerosis) AND Tema: (respiratory therapy)	270 (99)	49 reviews 2 repeats from Pubmed 47 do not fit the subject	1

Finally, after applying the inclusion and exclusion criteria, 19 valid articles were obtained for this study. Those clinical trials were subjected to the Jadad scale to evaluate their methodological quality, as will be explained later.

Results

In all the selected studies[6,8-25] different respiratory physiotherapy interventions are carried out to treat ALS. The results of the articles are presented below in different tables to facilitate reading and understanding.

Table 3 shows the characteristics and studies of the participants, including sample size, losses during the intervention or follow-up, age (mean and standard deviation or age range), sex (number of men and women) and the criteria for inclusion and exclusion of participants.

Table 4 shows the characteristics of the intervention carried out in terms of techniques and dosage, as well as the measuring instruments used, the results obtained and comparisons made within the same group and between the different groups in the study, if these data are provided, and the significance of the results obtained in each article.

The quality and methodological validity of the four clinical trials were evaluated according to the JADAD scale, obtaining scores of 0, 2, 4 and 5.

Table 2. Characteristics of study participants

Author	Sample size	Age	Sex	Losses	Inclusion criteria	Exclusion criteria
van Groenestijn et al.[8]	57 GI:27 GC:30	GI: 60,9±10 GC: 59,9±10,7	M:40 F:17	25 GI:17 GC:8	-ALS -18-80 years old -FVC≥ 80% -Diagnostic phase completed -life expectancy > 1 year -walking capacity (≥10 minutes) -cycloergometer capacity (≥15 minutes)	-patients who were already exercising≥ 2 hours per week. -severe cognitive impairment -Comorbidity -psychiatric disorder
Bédard et al.[9]	37	58±9,1	M:30 F:7	6	-ALS -Daytime orthopnea and hypercapnia -Symptoms of sleep-disordered breathing -FVC>50% of predicted -PI Max>40 cm H2O -Acute respiratory failure	-limited data
González Bermejo et al.[6]	74 GC:37 GI:37	GC:54(49-62) GI:60(51-66)	M:46 F:28	25 GC:7 GI:18	-ALS ->18 years old -FVCsitting>60% predicted but not >80% predicted -documented diaphragm responses to phrenic nerve stimulation	-indication of noninvasive mechanical ventilation at the time of detection -non-invasive pre-ventilation or continuous positive airway pressure -cardiovascular pathologies -obesity or chest deformity Pre-existing hernia of the diaphragm -respiratory tract infection or any acute event during the previous 2 months -pacemaker or defibrillator -breastfeeding and pregnancy -participation in any other clinical trial

Author	Sample size	Age	Sex	Losses	Inclusion criteria	Exclusion criteria
Bertella et al.[10]	50 IG Hospitalized: 25 IG Ambulatories: 25	IG Hospitalized: 65,92±10,18 IG Ambulatories: 61,26±8,64	M:31 F:19	14 IG Hospitalized:6 IG Ambulatories:8	-ALS -≥18 years old -no chest infections during the previous 3 months	-cognitive impairment -reluctance to participate -severe comorbidity -contraindications to NIV (cardiac arrhythmias, history of pneumothorax) -distance from hospital >40km or other problems to attend the outpatient clinic
Terzano et al.[11]	36 GI_1:20 GI_2:16	63,7±10,8	M:21 F:15	0	-ALS -pyramidal tract affectation -EMG evidence of diffuse impairment of anterior horn cells. -muscle weakness and atrophy in at least two non-contiguous muscle groups, lasting 6 months or more	-previous cerebrovascular events -arterial disease -ischemic heart disease -COPD -cancer -Acute respiratory failure -Tracheostomy -Inability to perform respiratory measurements
Sancho et al.[12]	47 G_1Spinal:28 G_2Bulbar:19	68,2±9,2	M:31 F:16	0	-ALS -medically stable for the previous 3 months	-refusal to participate in the study -bronchial disease -contraindication to the use of MI-E -severe frontotemporal dementia associated with ALS
Elamin et al.[13]	137 G_1Bulbar:29 G_2Cervical:45 G_3Lumbar:48 G_4Arm:5 G_5Leg:7 G_6PLS:3	62,31±11,37	M:131 F:6	0	-ALS ->18 years old -upper and lower motor neuron dysfunction in three or two body regions (bulbar or spinal)	-family history of ALS -history of chronic obstructive or restrictive pulmonary disease -fatal diagnosis preventing 6-month survival -Cognitive impairment
Magalhães et al.[14]	18 GC:9 GI:9	GI: 55±13 GC: 55±15	M:10 F:8	0	-ALS -non-smokers -no scoliosis or chest abnormalities -no clinical signs of bulbar muscle dysfunction -no history of tracheotomy -Ability to complete the tests without the use of NIV.	-inability to complete any of the test procedures
Boentert et al.[15]	65	63,1±11,7	M:36 F:29	54	-ALS -FVC< 50% -AHI > 5/h -SaO_2 < 90% ->10mmHg increase in $PtcCO_2$ from baseline on transcutaneous capnography -Nighttime $PtcCO_2$ >50mmHg -Daytime hypercapnia ($PaCO_2$> 45mmHg)	-

Author	Sample size	Age	Sex	Losses	Inclusion criteria	Exclusion criteria
Crescimanno et al.[16]	25 G_1Bulbar:11 G_2No bulbar:14	65,6±7,7	M:17 F:8	0	-ALS	mental disorder such as depression or dementia
Vitacca et al.[17]	194 GI_1LG:129 GI_2VEG:65	63,98±11,34	M:112 F:82	34	-ALS -respiratory insufficiency	-lack of spirometry data -NIV rejection -dementia -follow-up <36 months from diagnosis
Burkhardt et al.[18]	80	64±13,1	M:47 F:32	6	-Deceased ALS patients	-
Vrijsen et al.[19]	24 G_1Bulbar:10 G_2No bulbar:14	60±10	M:21 F:3	2	-ALS -PI Max<60 cmH2O / VC<80% -symptoms of nocturnal alveolar hypoventilation -PaCO2>45 mmHg or PtcCO2≥10 mmHg during sleep as compared to its awake supine value (≥ 40 mmHg)	-
Vandoorne et al.[20]	13	59(53-65)	M:11 F:2	0	-ALS -PI Max<60 cm H2O -FVC seated<80% -symptoms of nocturnal alveolar hypoventilation -PaCO2≥45 mmHg or PtcCO2≥10 mmHg during sleep compared to a normal awake supine value	-<18 years -unwillingness to start NIV
Dorst et al.[21]	58 G_1Espinal:39 G_2Bulbar:19	61(59-67)	M:30 F:28	55	-ALS -signos clínicos de insuficiencia respiratoria -FVC<80% -SNIP<40 cm H20 -PI Max<60 mm H20 -desaturación nocturna -$PaCO_2$<45 mmHg	-
De Mattia et al.[22]	43 IG_1Passive:23 IG_2Active:20	GI_1Passive: 54,6±12,4 GI_2Active: 63,8±8	M:24 F:19	0	-ALS -treatment with invasive mechanical ventilation initiated at the center after a recent tracheotomy -need of mechanical ventilation for 18 hours/day -use of a single limb circuit -Frequent use of closed ventilation through a cuffed tracheostomy tube. -regular follow-up, at least once a year	

Author	Sample size	Age	Sex	Losses	Inclusion criteria	Exclusion criteria
Vrijsen et al.[23]	35 G_1Bulbar: 18 G_2No bulbar:17	G_1Bulbar: 57±10 G_2No bulbar: 61±7	M26 F:9	0	-ALS -VC<80% of the predicted value -PI Max<60 cm H2O -symptoms of nocturnal alveolar hypoventilation -PaCO2≥45 mmHg during the day or PtcCO2≥10 mmHg during sleep compared to awake supine value	-starting in the intermediate intensive care unit -mask intolerance -severe cognitive impairment
Vrijsen et al.[24]	13 GI_1S-ST:7 GI_2ST-S:6	57±11	M:11 F:2	0	-ALS -VC<80% -PI Max<60 cm H2O -nocturnal hypoventilation -PaCO2≥45 mmHg during the day or PtcCO2≥10 mmHg during sleep compared to awake supine value	
McDermott et al.[25]	74 GI_1:37 GI_2: 37	GI_1: 54±12 GI_2: 60±10	M:58 F:16		-ALS ->18 years -Treatment with riluzole for at least 30 days -respiratory insufficiency -FVC<75% -SNIP<65cm H2O (men) or 55 cm H2O (women) -SNIP<40cm H2O -PaCO2>6 kPa (during the day) or 6·5 kPa (during the night) -acceptable bilateral phrenic nerve function	-prior use of non-invasive ventilation -pre-existing implanted electrical device -underlying heart disease or lung disease -current pregnancy or breast-feeding -inability to make decisions -obesity -significant scoliosis or deformity of the chest wall -pre-existing diaphragm abnormality -CVF<50% -nasal inspiratory pressure of less than 30 cm H_2O

Abbreviations: -: absent; AHI: Apnea/Hypopnea Index; UC: Usual Care; VC: Vital Capacity; FVC: Forced Vital Capacity; ALS: Amyotrophic Lateral Sclerosis; EMG: Electromyography; COPD: Chronic Obstructive Pulmonary Disease; F: Female; GX: Groups; CG: Control Group; IG: Intervention Group; M: Male; MI-E: Mechanical Insufflation-Exsufflation; PaCO2: Partial pressure of carbon dioxide; PIMax: Maximal Inspiratory Pressure; PLS: Primary Lateral Sclerosis; PtcCO2: Transcutaneous carbon dioxide; SaO2: Arterial oxygen saturation; SNIP: Sniff nasal inspiratory pressure; PET: Physical exercise therapy; NIV: Non-invasive ventilation.

Table 3. Physical therapy intervention characteristics, assessment and outcomes

Author	Study	Duration and Frequency	Intervention	Measuring Instruments	Results(p<0,05)
Van Groenestijn et al.	Randomized multicenter clinical trial	Follow-up: 4 visits in 10 months	IG:PET+UC: 16 weeks: 2 days/ week at home (20-35 minutes) and 1 day/ week individual trainng (1 hour) + multidisciplinary care CG:UC: multidisciplinary care	--ALSFRS-R -ALSAQ-40 -SF-36 -MCS -PCS -HRQoL -CIS -Spirometry	-Disease-specific HRQoL (ALSAQ-40): at 6 months significantly improved in favor of IG (p=0.046). -FVC: at 6 months differed significantly in favor of IG (p=0.048).
Bédard et al.[9]	Retrospective study	Study: from January 1996 to December 2012. Nocturnal NIV (12h/day): onset ranged from 43 days to 1,541 days, with a mean of 317 days. Daytime oral ventilation: onset ranged from 0 to 852 days, with a mean of 200 days.	VDaytime oral ventilation added to nocturnal NIV	-ALSFRS-R -Spirometry	-A peak cough flow with lung volume recruitment 180 L/min at the onset of mouth ventilation (peak flow decreased) was associated with increased survival (p=0.01). -ALSFRS-R: higher in subjects maintaining mouth ventilation (p=0.002).
González-Bermejo et al.[6]	Randomized multicenter clinical trial	Study: between September 27, 2012 and July 8, 2015. Phrenic stimulation: five times a day (30 minutes/day). After 10 days: gradual increase to 3 hours/day. Follow-up: 2 years	Phrenic stimulation CG: sham stimulation IG: active stimulation	-ALSFRS-R -Spirometry	--Mortality: higher in IG (p=0.026). -Median survival with free NIV was lower in IG (p=0.02). -Post-hoc analysis: ALSFRS-R during follow-up higher in CG (p<0.0001). -Post-hoc analysis: significant difference in ALSFRS-R before and after implantation of electrodes in IG (p<0.0001).
Bertella et al.[10]	Prospective randomized study	Study: March 2011 to March 2014 Follow-up: 3 months -T0: start -T1: end of NIV -T2: at three months follow-up of T1 NIV: at least 4 hours/day	NIV in outpatients and hospitalized patients	-ALSFRS-R -abG -BMI -Spirometry	-At t1, ambulatory patients had more hours of nocturnal ventilation (p<0.02). -Acceptance and adherence to NIV at T2 in all patients: higher in men (p=0.0007), spinal onset (p=0.027) and higher BMI (p=0.021).
Terzano et al.[11]	Non-randomized clinical trial	4 months (visits every 30 days) -T0: start -T1: 1° month -T2: 2° month -T3: 3° month -T4: 4° month	NIV IG1: NIV from time 0 IG2: patients who refused NIV at time 0 and subsequently started with worsening of symptoms and signs	-abG -Spirometry	-Statistically significant differences with respect to FEV1 (p<0,05), FVC (p<0,02), MIP (p<0,007), MEP (p<0,008) and TLC (p=0,007) in favor of IG1 at T4. The Tiffeneau Index is higher in IG2. (p<0,03). -Worsening of the IG2 group compared to the IG1 group, with respect to MIP. (from T1 p<0,05 to T4 p<0,007) and MEP (from T2 p<0,05 to T4 p<0,008). -FVC: higher in IG2 in T3 (p<0,04) and T4 (p<0,02). -Decrease in FEV1 in the IG2 group at T2 (p<0,05), T3 (p<0,05) and T4 (p<0,05). -T0-T1: the IG2 group had worse pH values (p<0,003), pCO2 (p<0,001), HCO3- (p<0,001), and lactate (p<0,002). -T2: the IG2 group had worse pH values (p<0,001), pCO2 (p<0,001), HCO3- (p<0,02) and lactate (p<0,006). Significant decrease in pO2 (p<0,001) and SO2 (p<0,001) in Group IG2. -T3: greater reduction in pH (p<0.001) and lower increase in pCO2 (p<0.001) in IG1 -T4: increase of pCO2 (p<0,02) in IG2's favor.

Author	Study	Duration and Frequency	Intervention	Measuring Instruments	Results(p<0,05)
Sancho et al.[12]	EsProspective study	EStudy: 2 years 4 treatment sessions	Cough-Assist with an insufflation pressure of 40 cm H2O, an exufflation pressure of 40 cm H2O and a 1-second pause (MI-E + HFO) in the spinal onset group (G1) and bulbar onset group (G2).	--ALSFRS-R -Norris scale -Spirometry	-Higher percentage of patients with effective peak cough flow in G1 (p<0.004).
Elamin et al.[13]	Cohort study	Study: from January 1, 2010 to December 31, 2014 AVAPS: minimum 8 hours/day	NIPPV (AVAPS) in patients with onset: G1Bulbar G2Cervical G3Lumbar G4Arm G5Leg G6PLS	-ALSFRS-R -Spirometry	-FVC%:post-AVAPS improvement sitting in G1 (p=0,001), G2 (p=0,012), G3 (p=0,0001), G4 (p=0,0001) and G5 (p=0,0001). -FVC%: post-AVAPS improvement supine in G1 (p=0,002), G2 (p=0,009) and G3 (p=0,0001).
Magalhães et al.[14]	Case series	Evaluations: two days each patient over a two-week period 1° day: inicial evaluation 2° day: seated and supine wall evaluation torácica	NIV (seated and supine) CG: without ALS IG: with ALS	-Spirometry	-Significant increase in Vcw (p=0.04), Veicw (p<0.01), Veecw (p<0.01), and VE (p=0.03) with the use of NIV in IG. -Vrcp% (p<0.01) and Vrca% (p<0.01) were significantly lower, while Vab% (p<0.01) was significantly higher in the supine position compared to the sitting position in both groups. -IG seated VE was associated with a significantly higher respiratory rate and lower Vcw than in CG.
Boentert et al.[15]	Retrospective study	Patients were discharged after application of NIV for 1-4 nights. Follow-up visits: -T0: PSG diagnosis -T1: first night at VNI -T2: 3 months -T3: 9 months -T4: 15 months.	NIV	-abG -AHÍ -ODI -ALSFRS-R -Spirometry	-T0: increases in slow wave sleep (p<0.01), rapid eye movement sleep (p<0.001), and oxygen saturation (p<0.0001). Decrease in AHI (p=0.001), respiratory rate (p<0.0001) and peak transcutaneous carbon dioxide tension (p<0.01). -T1: AHÍ (p=0,001), ODI (p<0,0001), SaO2 (p<0,0001) and t<90% (p<0,01) showed a significant improvement.
Vitacca et al.[17]	Retrospective observational study	Follow-up: 36 months Scheduled hours (every 2-6 months) NIV: minimum 4 hours/night	NIV IG1LG: subsequent NIV prescription with FVC<80% IG2VEG: early NIV prescription with FVC≥80%.	-Spirometry -abG	-Median survival from diagnosis to death was higher in IG2(p=0.0094) while the crude mortality rate was higher in IG1(p=0.022). -IG2 had a lower probability of death (p=0.001), which was significant in the non-bulbar group (p=0.007). At 3-year follow-up, tracheostomy was needed in a higher percentage of IG1 patients (p=0.009). The tracheostomy rate was higher in IG1 for the non-bulbar group and higher in IG2 for the bulbar group.
Burkhardt et al.[18]	Retrospective study	Study: between 2013 and 2015	NIV y PEG	-BMI	-Median diagnostic delay in patients with bulbar onset was 6 months shorter than in patients with spinal onset (p=0.05). It was significantly associated with shorter survival (p=0.01). -NIV significantly increased survival (p=0.01). -Bronchopneumonia: more frequent in patients with NIV (p<0.04), and even more frequent in patients with spinal onset (p<0.002). -The inclusion of PEG resulted in a significant increase in survival (p<0.01).

Author	Study	Duration and Frequency	Intervention	Measuring Instruments	Results(p<0,05)
Vrijsen et al.[19]	Prospective observational study	Study: from january, 2021 to april, 2013 Patients were admitted to the sleep laboratory for 5 days and 4 nights. One month after NIV, polysomnography was performed.	NIV during sleep in patients with sleep onset: G1Bulbar G2Nonbulbar	-Polysomnography -PSQI -ESS -SF-36 -McGillQoL -ALSFRS-R -abG -Spirometry	-ALSFRS-R at one month: decreased (p<0.01) for all patients; and for G1 and G2 (p<0.05). -Daytime PaCO2: significantly decreased in the total group (p<0.05) and G2 (p<0.05). -ESS: improvement post NIV in the total group (p<0.05) and G2 (p<0.05). -Sleep quality of G1 was better than in G2, with less stage 1 (N1) sleep, more REM sleep and lower AAI. -After one month: AAI and the percentage of N1 sleep were significantly reduced (p<0.01) in the total group and G2, and the percentages of N3 and REM sleep were significantly increased (p<0.05) in the same groups. -The total group showed improvement in AAI (p<0.01), N1 (p<0.01), N3 (p<0.01) and REM (p<0.05), while G2 showed improvement in SE (p<0.01), AAI (p<0.01), N1 (p<0.01), N3 (p<0.05) and REM (p<0.01). -The total group improved in time spent with SpO2%<90% overnight (p<0.01), N1 + N2 (p<0.01), REM (p<0.01) and PtcCO2>55 mm Hg (p<0.01) and N1 + N2 (p<0.05). -G2 improved in time spent with SpO2%<90% during total night (p<0.05), N1 + N2 (p<0.05) and REM (p<0.05) and time with PtcCO2>55 mm Hg during total night (p<0.01) and N1 + N2 (p<0.05). -G1 improved in time spent with SpO2%<90% during REM (p<0.05). -G2 showed improvements in daytime sleepiness (p<0.05), PSQI total score (p<0.01), McGillQoL total score (p<0.01). Bulbar patients improved in PSQI total score (p<0.01) and sleep duration (p<0.01). -SF-36 improvements for total (p<0.0001), G2 (p<0.01), and G1 (p<0.01). Vitality changed only for total (p<0.05) and G2 (p<0.01).
Vandoorne et al.[20]	Prospective observational study	Study: between February 2012 and May 2013 Follow-up: one year (re-evaluated in the outpatient clinic after 1, 3, 6, 9 and 12 months). NIV: 4 hours/day	NIV during sleep	Polysomnography -ESS -PSQI -SF-36 -McGillQoL -ALSFRS-R -Spirometry -abG	-ALSFRS-R: decrease at 3 months (p<0.05) and progressively up to 12 months (p<0.01). -SNIP: decrease at 9 months (p<0.01) and 12 months (p<0.05). -VC: decrease at 9 months (p<0.05) and at 12 months (p<0.01). -PaCO2: decrease at the first month (p<0.01), which is maintained up to 12 months. -NIV use: increase at 6 months compared to baseline (p<0.05). -IPAP: at 6 months was significantly higher compared to baseline (p<0.05). -SF-36: improvement in the short-term vitality subscale (p<0.05).
Dorst et al.[21]	Prospective study	Study: 14 months (August 2014 to October 2015). Follow-up: 24 months (every 3 months).	NIV in patients with onset G1Spinal G2Bulbar	-PSQI -SSS -BDI -CHS -NIVTS -ALSFRS-R -Spirometry -abG	-ALSFRS-R: significant decrease throughout the study in both groups. -G1 longer survival (p<0.064). -FVC≥80%: longer survival (p<0.01) in both groups. -BDI: higher in G2 (p=0.011). -At 3 months: improvements in PSQI (p=0.042), SSS (p=0.004) and CHS (p=0.013) in both groups. -At 6 months: worsening of PSQI (p=0.031) in both groups. -Mean ventilation times increased significantly at 3 months (p=0.045) and 6 months (p=0.037) of the two groups. -IPAP mean increased (p=0.027) after 3 months in both.
De Mattia et al.[22]	Retrospective study	Study: January 2012 to December 2014 Follow-up: one year NIV: 4 hours/day	NIV IG1: passive circuit IG2: active circuit	-ODI -Spirometry abG	--IG1 significantly differed from IG2 for mean age at disease onset (p<0.008) and for mean age at tracheostomy (p<0.007). -IG1: significant improvement of PaO2 at T1 and T2 compared to T0 (p<0.001). -Adverse event rate: higher in IG2 (p<0.001).

Author	Study	Duration and Frequency	Intervention	Measuring Instruments	Results (p<0,05)
Vrijsen et al.[23]	Prospective observational study	Study: between January 2012 and June 2014. NIV: three consecutive nights. Re-evaluated at one month Sleep, PVA and leakage assessed at discharge and after a month	NIV during sleep in patients with sleep onset: G1Bulbar G2Nonbulbar	Polysomnography -AHI -AAI -Spirometry -abG	-G2: improvements in sleep architecture (p<0.01), SpO2% (p<0.01) and nocturnal PtcCO2 (p<0.05) at discharge and at one month. -G1: significant improvement in SpO2% (p<0.01) during REM sleep. -AHI: decreased in both groups at discharge (p<0.05) and at one month (p<0.01). -AAI: improved in G2 (p<0.01) at discharge and at one month; and in G1 at discharge (p<0.05). -Leakage had an impact on the total amount of PVA in G2 at discharge (p<0.05) and after one month (p<0.05). In G1, a difference between PVA during leakage was found after one month (p<0.05).
Vrijsen et al.24	Prospective randomized crossover study	Study: between January 2012 and May 2013 Follow-up: every 3 months	NIV IG1:S-ST IG2:ST-S	-Polysomnography -ODI -AAI -abG	-ODI: lower in IG2 (p<0.05). -SpO2: higher in IG2 throughout the night (p<0.05), and during REM (p<0.05). -PtcCO2: higher in IG2 throughout the night (p<0.05) and during the different phases of sleep (p<0.05). -Ineffective efforts and respiratory events were more frequent in IG1 (p<0.01). -Survival was shorter in IG2 (p=0,006). -EQ-5D-3L: significant difference in favor of IG1 when a score of 0 was imputed after death (p<0.001).
McDermott et al.[25]	Randomized multicenter trial	NIV: minimum 4 hours/day Diaphragm stimulation: 6-7 hours/day Follow-up: at months 2, 3, 6, 6, 9 and 12 after randomization.	GI1: NIV GI2: NIV + diaphragm stimulation	-SF-36 -SAQLI -EQ-5D-3L	-Survival was shorter in IG2 (p=0,006). -EQ-5D-3L: significant difference in favor of IG1 when a score of 0 was imputed after death (p<0.001).

Abbreviations: AAI: Arousal-Awakening Index; abG: Arterial blood gas analysis; AHI: Apnea/Hypopnea Index; ALSAQ-40: Amyotrophic Lateral Sclerosis Assessment Questionnaire; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; AVAPS: Average Volume Assured Pressure Support; BDI: Beck's Depression Inventory; CHS: Clinic Hypoventilation Scale; CIS: Checklist Individual Strength; UC: Usual Care; FVC: Forced Vital Capacity; ALS: Amyotrophic Lateral Sclerosis; EQ-5D-3L: Euroqol 5D questionnaire 3-level format; ESS: Epworth Sleepiness Scale; FEV1: Forced expiratory volume in the first second; HCO3-: Bicarbonate; HFO: High-Frequency Oscilations; HRQoL: Health-Related Quality of Life; HRV: Heart Rate Variability; BMI: Body Mass Index; IPAP: Inspiratory Positive Airway Pressure; LG: Late Group; McGillQoL: McGill Quality of Life Questionnaire Simple Item Scale; MCS: Mental Component Summary; MI-E: Mechanical Insufflation-Exsufflation; N1: Stage 1 sleep; N2: Stage 2 sleep; N3: Slow wave sleep; NIPPV: Non-Invasive Positive Pressure Ventilation; NIVTS: Non-Invasive Ventilation Tolerance Score; ODI: Number of Oxygem Desaturations; PaCO2: Partial pressure of carbon dioxide; PaO2: Partial pressure of oxygen; PCS: Physical Component Summary; PEEP0: Initial Positive End-Expiratory Pressure; PEEP4: Final Positive End-Expiratory Pressure; PEG: Percutaneous Endoscopic Gastrostomy; MEP: Maximal Expiratory Pressure ; pH: Hydrogen Potential; MIP: Maximal Inspiratory Pressure; PSG: Polysomnography; PSQI: Pittsburgh Sleep Quality Index; PtcCO2: Transcutaneous carbon dioxide; PVA: Patient-Ventilator Asynchrony; REM: Rapid Eye Movement Sleep; RoC: FVC rate of change; SaO2: Arterial oxygen saturation; SAQLI: Sleep Apnea Quality of Life Index; SE: Sleep Efficiency; SF-36: Health Survey Short Form; SO2: sulfur dioxide; SpO2%: oxygen saturation; SSS: Stanford Sleepiness Scale; Tx: Times; PET: Physical Exercise Therapy; TLC: Total Lung Capacity; Vab%: Percentage of the contribution of the abdomen; Vcw: Chest Wall Volume; VE: Minute Ventilation; Veecw: Chest Wall End-Expiratory Volume; VEG: Very Early Group; Veicw: Chest Wall End-Inspiratory Volume; NIV: Non Invasive Ventilation; Vrca%: Percentage of the contribution of the abdominal rib cage; Vrcp%: Percentage of the contribution of the pulmonary rib cage

Table 4. Jadad Scale Score

Author	Alterorization	Description of randomization	Double blind	Blinding method	Description losses	Total score
van Groenestijn et al.8	1	1	0	1	1	4
González-Bermejo et al.6	1	1	1	1	1	5
Terzano et al.11	0	0	0	0	0	0
McDermott et al.25	1	1	0	0	0	2

Discussion

After an exhaustive review of the results, we will discuss them.

The type of study is highly variable: most of the studies are observational[9,13-15,17-21,23] and, to a lesser extent, experimental[6,8,10-12,16,22,24,25], of which only four are clinical trials[6,8,11,25]. In addition, we found five retrospective studies[9,15,17,18,22]. The reason why there are so many observational studies is that ALS patients need respiratory physiotherapy and it is a technique that is applied to them, so many authors limit themselves to observing what happens in the usual treatment of the disease. The methodological quality of clinical trials is assessed with the JADAD scale. A trial is considered to be of poor quality if its score is below 326. Therefore, the studies by Terzano, et al.[11] with a score of 0, and McDermott, et al.[25], with a score of 2, are of low quality, while those by VanGroenestijn, et al.[8] and González-Bermejo, et al.[6] are of high quality, with 4 and 5, respectively. The small number of RCTs in this review highlights the possible limitations of the research, since according to Donado Gómez, et al.[27], the randomized clinical trial is the best epidemiological study for evaluating the efficacy and safety of new interventions.

The sample size ranges from 13 participants in the articles by Vandoorne, et al.[20] and Vrijsen, et al.[24] to 194 in the article by Vitacca, et al.[17]. The remaining investigations[6,8-12,14-16,18,19,21-23,25] are between 18 and 80 participants, with Elamin et al.[13] standing out, with 137. These data indicate that the sample is not too varied, so the results are comparable. However, with a total sample of 1080 participants, it may not be sufficient to extrapolate the findings to the ALS-affected population. The mean age is similar in all the studies, around 60 years, with Magalhães, et al.[14] having the lowest mean and Sancho, et al.[12] the highest. These data correspond with the literature reviewed, which shows that ALS occurs between the ages of 58 and 63 for sporadic cases[1].

The male sex is dominant in all investigations, where the total number of males is 733, corresponding to 67.8% of the total, and the number of females is 347 (32.2%), which coincides with the prevalence of the disease, which is higher in males[1,13,28].

To determine treatment adherence, it is important to look at the losses in the investigations. These dropouts range from 7.5% in the study by Burkhardt, et al.[18] to 94.83% in the study by Dorst, et al.[21]. In the latter case, losses occur due to death or inability to attend the clinic due to progressive disability. These losses could have occurred for three reasons: they started NIV too late; NIV is not beneficial in cases of severe bulbar ALS; or the beneficial effects of NIV disappear in later stages of the disease leading to a worsening of the respiratory situation[21]. These losses pose a high risk of committing a selection bias. One reason may be the high number of studies that do not show exclusion criteria,[15,18,19,21,22,25] so that the patient selection filter is reduced. On the other hand, it is observed that many articles have no losses[11-14,16,20,22-25], which could mean that the treatment carried out generates good adherence or lacks side effects. Of the latter studies mentioned, only the one by De Mattia, tal.[22] is a retrospective study, which justifies the fact that there are no losses because they choose patients who have already completed treatment. In conclusion, a total of 221 losses occurred out of a total of 1080 participants (20.4%).

In the division into groups, we noticed that many studies have two intervention groups[10-13,16,17,19,21-25], while others have the presence of a control group[6,8,14]. The remaining studies show only one intervention group[9,15,18,20], thus being the base treatment for all the participants in the corresponding investigation.

As for the physiotherapy intervention used, NIV dominates[9-11,13-24]. However, in addition to NIV, daytime oral ventilation was added in the research conducted by Bédard et al.[9], PEEP by Crescimanno, et al.[16] and PEG in that conducted by Burkhardt, et al.[18]. In the study by Elamin, et al.[13] NIPPV is applied. ALS is characterized by respiratory muscle weakness and a progressive decline in lung function,[3] so the use of NIV can reduce the respiratory muscle load, consequently relieving dyspnea and improving gas exchange. It also avoids endotracheal intubation, which is a benefit for acute respiratory failure, the main cause of death in ALS[29]. Other interventions performed were phrenic stimulation by González-Bermejo, et al.[6] and McDermott, et al.[25], the application of the CoughAssist in the intervention performed by Sancho, et al.[12] and aerobic exercise in the study by Van Groenestijn, et al.[8].

Phrenic stimulation aims to cause muscular conditioning of this muscle, as well as to increase alveolar ventilation, increase pulmonary distensibility, or prevent atelectasis[6]. However, these studies[6,25] show that the results are negative. This may be due to the delay in the application of phrenic stimulation and/or the evolution of the patients. On the other hand, there is little research on this intervention in patients with LELA, so results cannot be compared, since, according to González-Bermejo, et al.[6], their research is the first controlled study on phrenic stimulation.

Patients with ALS lose their ability to clear their airways of respiratory secretions due to weakness of the respiratory musculature and dysfunction of the bulbar muscles, leading to insufficient or ineffective peak cough flow. The Cough Assist is intended to control respiratory secretions without having to resort to invasive methods, such as fibro bronchoscopy or even tracheotomy, in such a way that it facilitates the separation of thick secretions from the bronchial wall, allowing them to be cleaned and expelled[12].

The follow-up time varies. It ranges from one month according to Vrijsen et al.[23] to three years in the study by Vitacca et al.[17]. There are studies in which the follow-up time is not mentioned[9,13,16,18,19]. Follow-up is important because ALS involves chronic progressive degeneration. At the respiratory level, muscle weakness will eventually compromise ventilatory mechanics, causing dyspnea with relative hypoxia and, finally, respiratory failure[30]. Therefore, the objective is to make periodic revisions to assess the state of the pathology and avoid these complications, increasing the time of degeneration and, thus, the survival time. In addition, the participants may need lifelong respiratory treatment, so it would not be possible to make a follow-up after the end of the treatment. The time of application of the intervention varies. NIV is usually performed for 4 hours/day[10,17,20,22,25], 8 hours/day[13], 12 hours/day[9], or the time of NIV application is not mentioned[11,14-16,18,19,21,23,24]. The time of NIV application will depend on the patient's symptoms, tolerance, pulse oximetry, respiratory parameters, and blood gases. Patients who use NIV for more than 4 consecutive hours have a higher survival rate, so a minimum application of this time is recommended[31]. The use of longer NIV time manifests greater patient adherence and greater benefit, therefore, the results will be more optimal.

On the other hand, Van Groenestijn, et al.[8] applied physical exercise therapy three days a week for 16 weeks. In aerobic exercise, a 16-week pattern is established to observe improvements; however, in this type of treatment, an individualized and modifiable program should be carefully planned, taking into account the patient's needs[32].

Sancho, et al.[12] use the Cough Assist for four sessions. About this procedure, the number of applications will depend on the patient's needs, i.e. the amount of secretions present, to eliminate them.

In diaphragm stimulation, Gonzalez-Bermejo, et al.[6] applies it for 30 minutes/day, increasing it progressively until the patient endures 3 hours/day, and McDermott, et al.[25] applies it for 6 to 7 hours/day. However, no specific references can be found regarding the appropriate application time.

The different studies primarily evaluate ALS, quality of life and sleep quality. For the evaluation of ALS, the ALSFRS-R[6,8-10,12,13,15,16,19-21] and the ALSAQ-40[8], which are specific scales for this pathology, are used. The quality of life is manifested with the SF-368,[19,20,25],SAQLI[25], HRQoL[8], McGillQoL[19,20] and the EQ-5D-3L[25]. Regarding sleep, they applied the PSQI[19-21].

All the studies analyzed found beneficial results in terms of the application of the different physiotherapy techniques in the diverse parameters evaluated[8-24], except for the application of phrenic stimulation[6,25], as previously mentioned. Some studies do not have a control group[9-13,15-25], so the effect of the type of intervention cannot be verified. From the results, three lines can be drawn: studies with improvements in survival and quality of life and sleep; those with improvements mainly in respiratory parameters and arterial gases; and those with improvements in both.

Five studies[9,10,16-18] can be included in the first group, where increased survival is one of the main objectives, since ALS usually leads to death within 3 to 5 years[5], with bulbar ALS being more aggressive, where the evolution and survival time is 1 to 2 years[1]. These improvements are all equivalent to the application of NIV[9,10,16-18], with the inclusion of daytime mouth ventilation[9] and PEG[18].

It is necessary to differentiate between spinal-onset ALS and bulbar-onset ALS. The former is caused by degeneration of motor neurons in the spinal cord, and the first symptoms manifest in the extremities. Bulbar ALS affects the degeneration of the motor neurons of the brainstem, presenting dysarthria, dysphagia, and tongue twitching. The latter has a worse prognosis and progresses more rapidly[33].

The second group includes seven studies[11-15,22,24] whose improvements focus on respiratory and arterial gas parameters. This is relevant since respiratory failure is one of the main causes of death5. The predominant intervention in these studies is NIV[11,13-15,22,24], except in the study by Sancho, et al.[12], where Cough Assist is applied.

The latter group includes improvements in both aspects.[8] The research by Van Groenestijn, et al.[8], presents improvements in quality of life and FVC. Those performed by Vrijsen, et al.[19]. Vandoorne, et al.[20]. Dorst, et al.[21], and Vrijsen, et al.[23] show improvements at respiratory and gastric levels, and in quality

of life and sleep, in which NIV is applied during sleep[19,20,23], except for Dorst, et al.[21], which performs daytime NIV.

This being said, several limitations must be taken into account, such as the small sample of participants, the high percentage of males, the few studies with a control group, the scarcity of randomized clinical trials, and the lack of data. Likewise, it would be advisable to use the same assessment scales, thus unifying different criteria to standardize the results and make them more easily comparable. It would also be possible to standardize the variables analyzed and the measuring instruments used for assessment, for greater comparison of the results and a progression in the findings.

Conclusion

Respiratory physiotherapy appears beneficial in ALS patients in its different therapeutic variants.

Conflict of interest

Nothing to declare

Sources of financing

Nothing to declare

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