ORIGINAL ARTICLE

Meditation training for people with amyotrophic lateral sclerosis: a randomized clinical trial

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Background and purpose: Studies investigating psychological interventions for the promotion of well-being in people with amyotrophic lateral sclerosis (ALS) are lacking. The purpose of the current study was to examine the use of an ALS-specific mindfulness-based intervention for improving quality of life in this population.

Methods: A randomized, open-label and controlled clinical trial was conducted on the efficacy of an ALS-specific meditation programme in promoting quality of life. Adults who received a diagnosis of ALS within 18 months were randomly assigned either to usual care or to an 8-week meditation training based on the original mindfulness-based stress reduction programme and tailored for people with ALS. Quality of life, assessed with the ALS-Specific Quality of Life Revised scale, represented the primary outcome, whilst secondary outcomes included anxiety and depression, assessed with the Hospital Anxiety and Depression Scale, and specific quality of life domains. Participants were assessed at recruitment and after 2, 6 and 12 months. The efficacy of the treatment was assessed on an intention-to-treat basis of a linear mixed model.

Results: A hundred participants were recruited between November 2012 and December 2014. Over time, there was a significant difference between the two groups in terms of quality of life ($\beta = 0.24$, $P = 0.015$, $d = 0.89$). Significant differences between groups over time were also found for anxiety, depression, negative emotions, and interaction with people and the environment.

Conclusions: An ALS-specific meditation programme is beneficial for the quality of life and psychological well-being of people with ALS.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that affects upper and lower motor neurons. It is clinically characterized by progressive muscle atrophy, weakness, fasciculation and spasticity [1]. Life expectancy is generally 2–4 years from symptom onset, with only 5%–10% of patients surviving beyond 10 years [2]. It affects about two individuals per 100 000 every year, with an overall prevalence of five to six individuals per 100 000 [3].

Whilst current medical practice cannot stop the progression of the disease, the enhancement of quality of life (QOL) is considered the primary goal in ALS care [4]. Several psychological issues, including depression, hopelessness, distress, anxiety and fear of death, have

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been reported to be serious challenges to the QOL [5,6]. Although these issues have been extensively investigated through observational studies, there is an absence of controlled studies concerning interventions aimed to promote psychological well-being in this field [7]. Studies that examine how psychological well-being and QOL can be promoted with psychological interventions are urgently needed [8].

To date, some of the most promising clinical treatments for the reduction of distress, the improvement of psychological well-being and help for people dealing with a chronic disorder are based on the concept of mindfulness, which can be considered as the process of bringing attention to moment-by-moment experience, in a non-judgemental way, and by noticing how the present moment is novel, every time [9]. Mindfulness is reported to be associated with higher QOL in both ALS patients [10] and their caregivers [11]. In general and clinical populations, common interventions for the promotion of psychological well-being through mindfulness utilize meditation. Specifically, the most commonly used training programme is Mindfulness Based Stress Reduction (MBSR), developed by Jon Kabat-Zinn [12]. The goal of this training programme is to bring the attention to the present moment ('what I am doing now; how I feel now') and accept feelings, sensations and emotions, without judgement. This allows people to better manage their feelings and emotions, and improves their ability to accept their illness [12]. The practice of meditation leads to an awareness of what is happening in the body and the achievement of a more balanced emotional state. It also increases the ability to remain physically passive (i.e. without movement) for long periods of time and maintain a positive experience.

A specific meditation training programme based on the original MBSR protocol was developed and was adapted for people with ALS to better address illness-related challenges and to be sensitive to clinical peculiarities, in a way that the original protocol was not designed to do [13]. In fact, each of the eight weekly group sessions emphasizes accepting the discomfort and physical limitations of ALS, focusing on the resources and abilities that are available. Arguments, metaphors and sharing moments amongst participants are adapted to the daily reality of people with ALS. Participants are invited to explore, non-judgmentally, their emotions and the possibility that physical limitations can lead to stress, with particular attention to the expression of anger. Physical exercises, such as Hatha yoga (yoga postures) or mindful eating (chewing a raisin fully aware of perceptions and feelings), have been removed or changed to make them appropriate for a functionally impaired ALS population. Primary caregivers (one for each patient) are also invited to join the intervention.

The current study seeks to test the efficacy of this mindfulness training that was developed for the promotion of QOL and reduction of distress.

Methods

Study design and participants

A randomized, open-label and controlled clinical trial was conducted of the efficacy of an ALS-specific mindfulness training programme in promoting QOL compared to usual care, with a 1-year follow-up, which involved an overall sample of 100 ALS patients.

Recruitment and intervention were conducted in a hospital setting, a clinical centre specialized in the treatment and management of neuromuscular disorders (NEMO – Neuromuscular Omnicenter, Milan). Study approval was obtained by the Ethics Committee of Niguarda Ca' Granda Hospital. The study protocol was registered in the ISRCTN registry, with the ID no. 88066803.

Individuals were considered eligible when they met the following inclusion criteria: probable or definite ALS diagnosis according to El Escorial criteria [14]; aged 18 years or older; an Amyotrophic Lateral Sclerosis Functional Rating Scale Revised score above 24; ALS diagnosis within 18 months; the ability of the patient to speak and understand; and no secondary severe comorbidity, including significant cognitive and/or behavioural impairment, as assessed by the study physicians. Patients with a personal history of psychiatric disorders, as assessed by medical records and clinical interviews, were also excluded. All participants provided written informed consent before the baseline assessment or, for individuals unable to write, verbal consent was given and a witness signed to acknowledge the consent of the participant.

Randomization

Participants were randomly assigned 1:1 to join the meditation programme (intervention group) or to receive usual care (control group) using a web-generated (www.random.org) random list.

Procedures

Participants in the experimental group joined an 8-week ALS-specific meditation programme, mentioned earlier, based on the original MBSR protocol [12] and adapted to ALS clinical features (MBSR-ALS). The

full clinical protocol was previously reported by our group [13].

Controls received usual care and were not invited to join the intervention afterwards. Usual care was provided in a multidisciplinary setting and it also included individual counselling and psychological support when requested.

Participants from both conditions were assessed at recruitment (T0, baseline), after 2 months (T1, post-intervention for the experimental group) and after 6 (T2) and 12 (T3) months.

Outcomes

The primary study outcome was QOL, assessed with the ALS-Specific Quality of Life Revised (ALSSQoL-R) [15], which is a questionnaire specifically developed to assess QOL in people with ALS. It is composed of 46 items and each question is rated with a 10-point Likert scale. Together with the total average score (0–10), which represents the primary outcome, the scale produces a single-item QOL score and six domain scores: negative emotion, interaction with people and the environment, intimacy, religiosity, physical symptoms and bulbar symptoms. All of these domains represent secondary outcomes.

Secondary outcomes included depression and anxiety. They were assessed with the Hospital Anxiety and Depression Scale (HADS) [16], a questionnaire designed to screen for the presence and severity of depression and anxiety over the previous week in medical patients. It has a seven-item depression subscale (HADS-D) and a seven-item anxiety subscale (HADS-A), both on a four-point Likert scale (range 0–3). Each subscale score is the sum of the respective seven items (ranging from 0 to 21). The scale is composed primarily of items unrelated to somatic symptoms of depression and anxiety, reducing the interference of physical components that could confound the results [6].

Dispositional trait mindfulness was assessed as a potential moderator of the results. It was measured with the Five Facet Mindfulness Questionnaire (FFMQ) [17]. The FFMQ is a 39-item scale assessing five components of mindfulness: observing, describing, acting with awareness, non-judging and non-reacting.

Statistical analysis

Data were analysed on an intention-to-treat basis with the multilevel growth modelling technique [18]. Time (four repeated measures coded as follows: 0 = baseline; 1 = 2 months (post-treatment); 2 = 6 months; 3 = 12 months after the end of treatment), mindfulness (time-varying), treatment (0 = control; 1 = treatment) and the interactions time × mindfulness and time × treatment were included in all growth models (one for each outcome) using a bottom-up approach starting from a generalized least squares model. All fixed effects were tested step by step by means of the t test based on the Satterthwaite approximation for degrees of freedom or the Wald t test, whilst random effects were tested with the likelihood ratio test. Also, the covariance and error structures of the models were assessed step by step. In particular, it was determined whether model fits improved on incorporating (i) an autoregressive structure with serial correlations, (ii) heteroscedastic residuals for each time point and (iii) heteroscedastic residuals for each time point in each condition. Treatment effect size was finally calculated for each outcome using the following formula [18]: the ratio of the time × treatment coefficient to the square root of the estimated slope variance. All models were fitted by maximum likelihood. Critical alpha was set to 0.05 for all statistical tests. R software (release 3.1.2) and RStudio (version 0.99.441; RStudio Inc.) were used for model fitting, in particular the R packages lmerTest (version 2.0-30) and nlme (version 3.1-119).

Power analysis and sample size

Given the novelty of the trial (no other study has ever assessed the efficacy of a psychological intervention on ALS patients' QOL and well-being) and the multilevel approach that was planned for use for data analysis, the necessary parameters for proper power analysis (i.e. between-subject slope variance and error variance) were not available at the time of study planning; therefore, sample size was calculated for a medium-size interaction effect ($f = 0.25$) in a 2 (between) × 4 (within) mixed ANOVA. G*Power software (release 3.1.3) [19] was used, and the output showed that, setting alpha to 0.05, power to 0.95, the correlation amongst repeated measures to 0.5 and the non-sphericity correction to the lowest value (0.34), a total sample size of 80 was needed to detect the hypothesized effect with the desired power. Taking into account a possible dropout rate of 25%, the number of patients to be recruited was further increased to 100.

Results

A hundred ALS patients out of 300 eligible were recruited in the period between November 2012 and December 2014. After baseline assessment, they were randomly assigned to receive usual care or to join the

meditation training. All the information about the patients' participation and dropout rates are reported in Fig. 1.

The clinical and psychological baseline characteristics of the sample are shown in Table 1. No significant differences were detected between the two groups at the baseline.

Unconditional growth models

Each outcome was first regressed on time in a growth model with a random intercept. The likelihood ratio test showed that all growth models with a random intercept were significantly better than their counterparts without random intercepts. With the exception of the ALSSQoL-R single item scale, ALSSQoL-R intimacy, and ALSSQoL-R religion, whose average trends were quite flat – the fixed linear effects of time were statistically significant in all other models, showing that, on average, negative outcomes (anxiety and depression) increased along time, whilst positive outcomes (ALSSQoL-R total score and subscales) decreased. A random slope was then added to all models and the likelihood ratio test indicated that the random linear effect of time was statistically significant for depression, ALSSQoL total score, negative emotions, interactions and religion. Quadratic trends were also tested but did not significantly improve the fit of any model. Autocorrelation and heterogeneity of residuals over time were finally assessed by incorporating autoregressive and heteroscedastic error structures. Only the model predicting ALSSQoL interactions was significantly improved by allowing for autocorrelation, whilst models predicting anxiety and depression were improved by modelling heteroscedastic residuals for each time point.

Conditional growth models

Mindfulness was the first predictor to be included in the models that passed the first step. Since the first

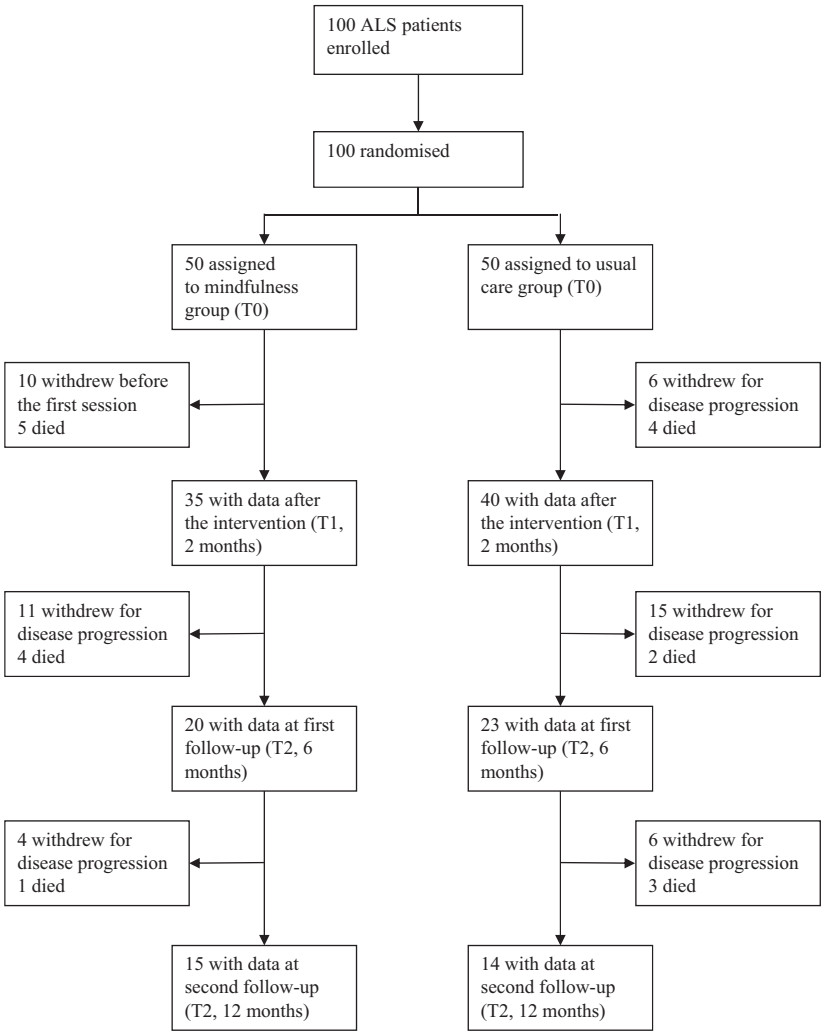

Figure 1 Study profile.

Table 1 Baseline characteristics

	Meditation (n = 50)	SD	Usual care (n = 50)	SD
Sex				
Male (0)	31		33	
Female (1)	19		17	
Age	57.933	11.330	63.411	10.156
Time since symptom onset (months)	11.642	15.773	11.381	14.755
ALSFRS	29.833	4.834	32.167	6.645
Quality of life	5.859	1.112	5.621	1.051
Anxiety	7.840	3.222	7.242	3.662
Depression	5.861	2.770	6.363	2.841
Quality of life (single-item scale)	5.775	1.950	5.776	2.365
Negative emotion	5.938	1.508	5.701	1.544
Interaction with people and the environment	7.338	1.638	7.342	1.413
Intimacy	5.657	2.179	5.149	1.744
Religiosity	5.425	2.910	5.371	3.599
Physical symptoms	6.251	2.155	6.081	1.917
Bulbar symptoms	6.772	2.731	6.124	2.470
Mindfulness	3.623	0.429	3.510	0.499

ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale.

time period was coded as 0, its main effects represented the cross-sectional correlations between the baseline scores of mindfulness and the baseline scores of each outcome. The t test based on the Satterthwaite approximation for degrees of freedom showed that, at baseline, mindfulness was significantly related to anxiety, depression and ALSSQoL religion with a negative sign, and to ALSSQoL total score, negative emotions, interactions and intimacy with a positive sign. An interaction between time and mindfulness was then included but was not statistically significant in any model. Finally, treatment and its interaction with time were included.

Whilst the main effect represents the baseline difference in each outcome between the two conditions, the interaction effect is the between-group difference between the means of the slopes and reflects the degree to which treatment moderated the effect of time. All models were first extended by allowing for heteroscedastic residuals for each time point in each condition. This significantly improved only the fit of the model predicting depression. Given that no statistically significant difference between conditions was found in any outcome variables at baseline, only interaction effects were examined, and the results showed that the meditation training was effective in reversing the decreasing trend of ALSSQoL-R total score (β = 0.24, P = 0.015, d = 0.89, Fig. 2), and the increasing trends of depression (β = 0.93, P = 0.013, d = 1.06, Fig. 3) and anxiety (β = 0.96, P = 0.038, d = 0.78, Fig. 4). Similarly, those who joined the meditation training showed improved trends on ALSSQoL-r negative emotions (β = 0.38, P = 0.018, d = 0.91) and ALSSQoL-R interactions (β = 0.43, P = 0.009, d = 1.49). A statistically significant treatment × time interaction was also found in the model predicting the ALSSQoL single item (β = 0.49, P = 0.01, d = 11.17). Table 2 gives the fixed and random coefficients of the final models.

Discussion

Our results indicate that ALS-specific meditation training improves the QOL of people with ALS. Furthermore, in comparison with those who received the standard care, participants who joined the MBSR-ALS course reported lower levels of anxiety and depression. These results confirm the initial hypothesis. To our knowledge, this is the first randomized

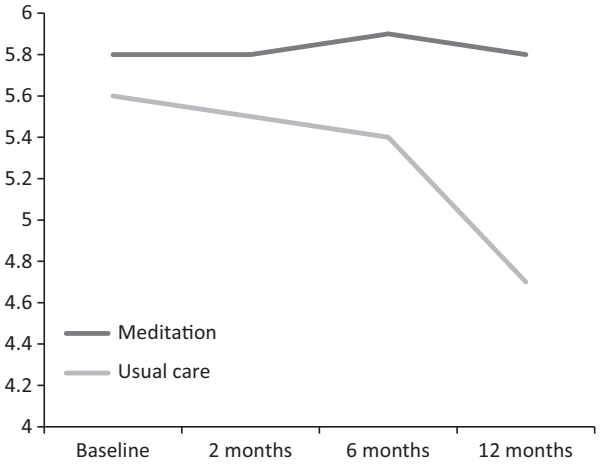

Figure 2 Quality of life (ALSSQOL-R) scores.

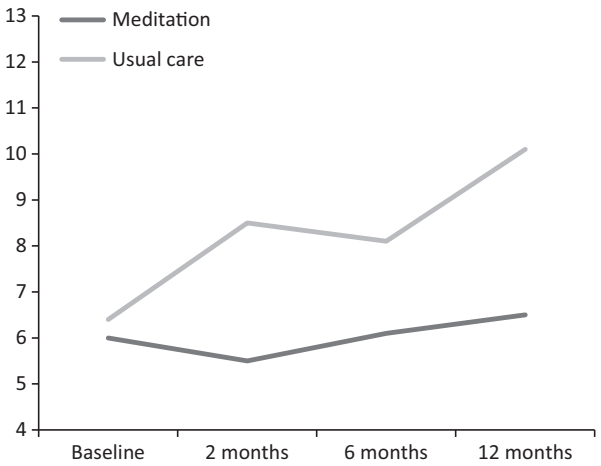

Figure 3 Depression (HADS-D) scores.

Table 2 Conditional growth models

	Fixed	t (df)[a]	P	Random[b]	Error structure
Quality of life (ALSSQoL-R)					
Intercept	4.14	10.696 (235.66)	0.0000	0.93	ns
Time	−0.22	−3.302 (56.72)	0.0017	0.27	
Mindfulness	0.43	4.268 (204.32)	0.0000		
Treatment	0.14	0.657 (99.26)	0.5125		
Time × treatment	0.24	2.513 (54.3)	0.0149		
Residual				0.55	
Anxiety (HADS)					
Intercept	11.81	6.936982 (143)[2]	0.0000	2.59	b
Time	0.98	3.108609 (143)[2]	0.0023	1.22	
Mindfulness	−1.29	−2.792732 (143)[2]	0.0059		
Treatment	0.66	0.989514 (98)[2]	0.3248		
Time × treatment	−0.96	−2.094526 (143)[2]	0.0380		
Residual				2.13	
Depression (HADS)					
Intercept	9.68	7.803122 (143)[2]	0.0000	2.08	c
Time	1.03	3.835342 (143)[2]	0.0002	0.87	
Mindfulness	−0.90	−2.686089 (143)[2]	0.0081		
Treatment	−0.85	−1.536291 (98)[2]	0.1277		
Time × treatment	−0.93	−2.523899 (143)[2]	0.0127		
Residual				1.57	
Quality of life (ALSSQoL-R single-item scale)					
Intercept	5.81	20.396 (102.97)	0.0000	1.56	ns
Time	−0.33	−2.449 (155.03)	0.0154	0.04	
Treatment	0.18	0.444 (104.31)	0.6583		
Time × treatment	0.49	2.584 (152.67)	0.0107		
Residual				1.4	
Negative emotions					
Intercept	3.55	5.930 (240.1)	0.0000	1.23	ns
Time	−0.36	−3.329 (54.41)	0.0016	0.42	
Mindfulness	0.65	4.116 (220.38)	0.0000		
Treatment	−0.03	−0.114 (99.25)	0.9098		
Time × treatment	0.38	2.446 (52.09)	0.0179		
Residual				0.88	
Interaction					
Intercept	4.79	8.089575 (143)	0.0000	0.77	a
Time	−0.20	−1.747490 (143)	0.0827	0.29	
Mindfulness	0.74	4.679617 (143)	0.0000		
Treatment	−0.15	−0.503921 (98)	0.6154		
Time × treatment	0.43	2.613074 (143)	0.0099		
Residual				1.24	
Intimacy					
Intercept	2.53	2.934 (245.62)	0.0037	1.20	ns
Time	0.13	0.946 (152.63)	0.3457	0.05	
Mindfulness	0.71	3.040 (241.31)	0.0026		
Treatment	0.63	1.759 (106.86)	0.0815		
Time × treatment	−0.04	−0.205 (147.93)	0.8378		
Residual				1.47	
Religion					
Intercept	8.69	5.979 (24.3)	0.0000	2.31	ns
Time	−0.10	−0.352 (41.54)	0.7276	1.14	
Mindfulness	−0.84	−2.156 (231.64)	0.0321		
Treatment	−0.41	−0.647 (98.67)	0.5192		
Time × treatment	0.29	0.687 (49.08)	0.4961		
Residual				2.35	

(continued)

Table 2 *(Continued)*

	Fixed	t (df)[a]	P	Random[b]	Error structure
Physical symptoms					
Intercept	5.96	21.909 (100.37)	0.0000	1.74	ns
Time	−0.41	−4.159 (48.09)	0.0001	0.23	
Treatment	0.27	0.699 (100.87)	0.4861		
Time × treatment	0.06	0.420 (43.31)	0.6767		
Residual				0.90	
Bulbar symptoms					
Intercept	6.14	17.545 (97.88)	0.0000	2.16	ns
Time	−0.46	−2.792 (34.97)	0.0084	0.56	
Treatment	0.82	1.655 (98.59)	0.1011		
Time × treatment	0.25	1.049 (33.28)	0.3018		
Residual				1.35	

ALSSQoL-R, Amyotrophic Lateral Sclerosis Specific Quality of Life Revised; HADS, Hospital Anxiety and Depression Scale. Error structure: ns, not significant; a, autoregressive structure with serial correlations; b, heteroscedastic residuals for each time point; c, heteroscedastic residuals for each time point in each condition. With the exception of anxiety, depression and interaction, all other t tests used Satterthwaite approximations to degrees of freedom; [b]Standard deviation.

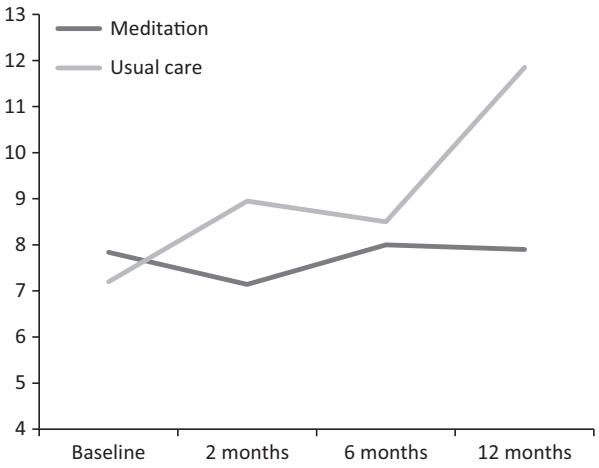

Figure 4 Anxiety (HADS-A) scores.

clinical trial that has investigated the effects of a psychological intervention on the QOL of people with ALS. Despite the need for an exploration of the effects of psychological treatment in the promotion of well-being [7], the available information is currently limited [8]. Recent quasi-experimental, non-randomized or limited-sample studies suggest that cognitive-behavioural therapy [20], hypnosis [21], expressive disclosure [22] and dignity therapy [23] may all increase QOL and psychological well-being. There is currently insufficient evidence, however, to recommend the use of a specific psychological intervention for the promotion of well-being in ALS [8].

Mindfulness-based interventions are currently some of the most commonly used psychological interventions to improve QOL in people with chronic diseases [9], but no study has explored their effects in the ALS field. Subjective feedback was previously reported from a subsample of participants of the current study who joined the meditation training, with a qualitative approach [24]. The interviewed patients reported more functional coping strategies and an improvement in resilience following the training. Specifically, they described a reduction in a judgemental attitude, increasing the disposition towards acceptance. These two aspects seem particularly relevant for people with ALS as they are forced to cope with the changes in the disease, which are often unpredictable and negatively evaluated. One of the main mechanisms of change that leads meditation to improve psychological well-being is the cultivation of mindfulness as a mental state [9]. Mindfulness is a multifaceted construct, which includes being in the present moment, awareness, flexibility, openness and curiosity. All these aspects have been reported to support psychological well-being, distress tolerance and resilience [25]. The current study results are in line with these preliminary findings and they provide evidence of positive effects across different aspects of psychological well-being and QOL. Furthermore, differences between the two groups remained stable or increased through time.

Despite findings from a previous study [10] that suggested a negative relationship between mindfulness and disease progression, no effect of meditation on physical impairment was found. This was not expected or anticipated in the study hypothesis, as the treatment focused on the acceptance of symptoms, as well as emotions and feelings. The question whether psychological interventions can affect the course of the disease remains unanswered.

Several limitations of this investigation require mention. First, the control group did not receive any additional treatment to the usual care. Patients may have improved simply because they received more attention or because they had more opportunity to share their emotions with a group of other patients. These results need to be confirmed by studies with an active control group. The usual care for controls was chosen because, at the time the project was designed, there was no study at all that explored psychological interventions. The comparison gold standard was, and still is [26], multidisciplinary care, which may include a psychologist or a social scientist who can support patients and their caregivers when requested. Therefore, no structured intervention was available as a comparison. Secondly, the recruitment process was very challenging. Several patients reported a lack of interest, if not opposition, towards the idea of a psychological intervention, or logistical reasons that prevented their participation in the trial. These are important issues that should be considered when discussing the clinical feasibility and reproducibility of the intervention. Thirdly, there was a high attrition rate, although it seemed similar to other longitudinal non-pharmacological studies conducted in the ALS field (i.e. [27]) and may be expected, given the degenerative nature of the disease.

Despite some limitations, the study is one of the first contributions that provides evidence of the effects of a psychological intervention in the promotion of QOL in people with ALS. Further investigations about the effects of psychological and psychotherapeutic programmes are warranted. This ALS-specific mindfulness-based intervention could be used as a comparison for future studies that will explore the effects of other treatments. Furthermore, future studies may investigate the underlying neurological mechanisms that change after a psychological intervention, to explore possible interactions with the disease progression mechanisms. Similarly, on a clinical level it may be worth investigating the potential effects of psychological interventions on the perception of symptoms (e.g. pain), as well as possible neurological processes that can mediate the effects of cognitive and emotional outcomes over the course of the disease.

The clinical implications of the study could be relevant in terms of QOL and well-being promotion. Considering that maintaining a high QOL is the primary goal of ALS care [4], this aspect seems particularly important. The protocol is publicly available [13] and further information can be requested from the authors. The ALS is safe and easy to implement, as it can be conducted by trained personnel and does not require additional instruments. It can be integrated in current multidisciplinary care and may represent a new way to enhance the QOL in people with ALS.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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