**Psychotherapy and pharmacotherapy interventions to reduce distress or improve wellbeing in people with amyotrophic lateral sclerosis: A systematic review**

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**Running title:** Review of psychotherapy and pharmacotherapy in ALS

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**Word count:** 3270

**ABSTRACT**

*Objective:*

To systematically review and critically evaluate the evidence for psychotherapy and pharmacotherapy interventions for reducing distress or improving wellbeing in people with amyotrophic lateral sclerosis (pwALS).

*Methods:*

Online bibliographic databases and clinical trial registers were searched and an assessment of study quality was conducted.

*Results:*

7223 studies were identified, of which five met inclusion criteria (four completed and one in progress). All studies examined psychotherapeutic interventions, and no studies investigated pharmacotherapy. Two studies adopted a randomised controlled trial design, one a controlled trial design and two a cohort design. Sample sizes were small in all studies (overall N=145). The quality of completed studies was generally poor, with evidence that all were at potential risk of bias in numerous areas. Improvements in wellbeing were found with expressive disclosure (in comparison to no disclosure), Cognitive Behavioural Therapy/counselling (compared to non-randomised pharmacotherapy) and hypnosis in the short-term only, while no improvements were seen with a life review intervention.

*Conclusions:*

There is currently insufficient evidence to recommend the use of specific psychotherapy interventions for reducing distress or improving wellbeing in pwALS, and no evidence to support pharmacotherapy interventions. Research is urgently needed to address these significant gaps in the literature.

**Word count:** 197

**KEY WORDS:** Amyotrophic lateral sclerosis, psychotherapy, pharmacotherapy, distress, wellbeing

**INTRODUCTION**

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive fatal neurodegenerative disease for which there is no cure, prognosis is poor, and median survival is 2-3 years following symptom onset1. Given its devastating consequences, it is unsurprising that some pwALS may experience distress during the course of the condition (e.g. low mood, fearfulness, hopelessness, pessimism, loneliness and despair). Estimated prevalence rates of depressive and anxiety disorders vary markedly from 0-44% for minor or major depression and 0-30% for anxiety, although rates vary depending on how they are assessed2-4. For example, mood disorders may be under- or over-identified depending on the use of self-report measures vs. structured psychiatric interviews (lower rates have been reported for the latter2-3), degree of inclusion of somatic symptoms which may overlap with ALS symptoms (higher rates have been reported for self-report measures that put greater emphasis on somatic symptoms4), and use of non-optimal cut-offs that may lack specificity2,4-6. Other factors include methodological limitations such as the degree to which prevalence studies assess the current use of pharmacotherapy or psychotherapy (as lower rates may be reported in those undergoing such treatment) and the use of non-representative samples2. Although prevalence rates for depression may appear to be lower than in other neurodegenerative conditions such as Parkinson’s disease (PD), Huntington's disease and multiple sclerosis (MS), they are comparable to other neuromuscular disorders with comparable disease profiles, and are higher than those found in the general population4.

One important potential outcome for pwALS is an increased risk of assisted/non-assisted suicide. A study in Sweden reported that the relative risk of suicide was almost six times greater in pwALS than in age- and gender-matched individuals in the general population7; a figure higher than reported in MS, PD and malignant cancers. Furthermore, pwALS appear to be at particular risk of suicide and suicidal ideation following diagnosis and in the year following the first period of hospitalisation7-8. The contribution of mood disorders to increased suicide risk is likely to be complex as some prospective studies have shown that wishes to hasten death or requests for euthanasia/assisted suicide are associated with depression and/or anxiety9, while others have not10. Another study reported higher scores for suicidal ideation, demoralization and hopelessness in pwALS compared to metastatic cancer, despite comparable scores for depression11. Indeed, feelings of loneliness, low quality of life, perceptions of being a burden on others and hopelessness appear to be other important determinants9,12-13, suggesting that such feelings are valid targets for treatment even in the absence of clinical depression or anxiety disorder.

Even in those who do not choose to shorten their own lives, distress is associated with an increased risk of mortality and poorer quality of life. One study reported an almost seven times greater risk of mortality in pwALS experiencing distress compared to those experiencing wellbeing14, while another reported that low mood at 6-weeks post-diagnosis predicted poorer survival at 6 months15. In addition, significantly shorter median survival times have been found in those experiencing distress compared to those with high levels of wellbeing (333 vs. >1200 days, respectively), together with a poorer quality of life14,16.

Given these associations between distress and risk of suicide/mortality/poorer quality of life, it is imperative that distress is adequately treated in pwALS. However, relatively little is known about how this might be achieved. Current recommendations for the management of depression and anxiety in adults with chronic physical health conditions and terminal illness include treatment with pharmacotherapy (e.g. antidepressants or anxiolytics), psychotherapy (e.g. Cognitive Behavioural Therapy [CBT]), or a combination of both depending on the severity of the disorder17-20. Guidelines issued by the European Federation of Neurological Societies (EFNS) Task Force on Diagnosis and Management of ALS21 state that depression should be treated with an appropriate antidepressant (e.g. amitriptyline, mirtazapine or a selective serotonin reuptake inhibitor), while anxiety should be treated with bupropion or benzodiazepines, though no evidence has been cited to support these recommendations. Furthermore, no recommendations were made in relation to psychotherapy. Others have suggested that modifications or adjuncts to conventional CBT may be of value in addressing the particular psychological needs of pwALS3, though evidence to support these proposals is lacking. Certainly, a lack of research on the efficacy of psychological interventions for pWALS has previously been noted22. Consequently, the aims of this review were to systematically review and critically evaluate the evidence for psychotherapy and pharmacotherapy interventions for reducing distress or improving wellbeing in pwALS.

**MATERIAL AND METHODS**

**Identification of studies**

Online bibliographic databases (MEDLINE 1946-present, Embase 1947-present, PsychINFO 1806-present, and CINAHL 1981-present) were searched on 20 November 2014 using the following terms:

1. ((("amyotrophic lateral sclerosis" OR "motor neuron disease" OR "motor neurone disease" OR "Lou Gehrig's disease") and (psychotherap\* OR "psychological therapy" OR "psychological therapies" OR psychosocial OR counselling OR counseling)) NOT ("genetic counselling" OR "genetic counseling")));

2. (("amyotrophic lateral sclerosis" OR "motor neuron disease" OR "motor neurone disease" OR "Lou Gehrig's disease") and (depression OR depressed OR depressive OR anxiety OR anxious OR "psychological distress" OR “psychological wellbeing” OR “psychological well being” OR “psychological well-being”));

3. (("amyotrophic lateral sclerosis" OR "motor neuron disease" OR "motor neurone disease" OR "Lou Gehrig's disease") and (antidepressant OR anti-depressant OR anxiolytic)).

All fields were searched including medical subject headings. In addition, the terms "amyotrophic lateral sclerosis" OR "motor neuron disease" OR "motor neurone disease" OR "Lou Gehrig's disease" were used to search the following databases and registers: Cochrane Central Register of Controlled Trials; WHO International Clinical Trials Registry Platform (a search portal containing data from 15 international clinical trial registers); and Open Grey (an online grey literature database). References of published reviews and studies were also manually searched.

**Inclusion/exclusion criteria and study selection**

Studies were included if they met the following criteria:

1. Evaluated any type of study design (e.g. randomised controlled trial design [RCT], controlled trial [CT], cohort study or case-control), with the exception of case reports;

2. Included participants with a diagnosis of ALS;

3. Involved a form of psychotherapy or pharmacotherapy aimed at reducing distress or improving wellbeing (where distress or wellbeing was included as a primary outcome measure). Psychotherapy was defined as any face-to-face or self-help intervention employing common psychotherapeutic techniques such as cognitive restructuring, psycho-education, guided visual imagery, life review, or facilitation of emotional expression;

4. Published in any language as a journal article, conference abstract, dissertation or thesis.

Titles and study abstracts were initially screened in order to determine eligibility for retrieval. Retrieved articles were then screened for eligibility and selected for inclusion using a structured pro-forma. Studies were independently screened and selected by two authors (RLG and MCC), and disagreements were resolved through discussion.

**Assessment of study quality and data extraction**

Study quality was assessed using the Cochrane Collaboration’s Risk of Bias Tool23, which assesses study quality in five areas of bias known to affect clinical outcomes: sequence generation, allocation concealment, blinding of participants/outcome assessors, incomplete outcome data, and selective outcome reporting. The quality of studies was independently rated by two authors (RLG and MCC), with disagreements being resolved through discussion. Potential sources of patient heterogeneity and factors that may confound or influence the interpretation or generalisability of results were also identified in each study. In addition, data on a range of clinical and research variables were independently extracted from each study by two authors (RLG and MCC), and discrepancies were resolved through discussion.

**RESULTS**

**Study characteristics**

7223 studies were identified. Of these, five were selected after screening24-30. Four studies have been completed to date24,26-29 and one is in progress30 (see Figure 1 and Table 1). All studies examined psychotherapeutic interventions, and no studies investigated pharmacotherapy. Two additional studies failed to recruit pwALS: one open-label phase III trial attempted to explore the use of escitalopram for major depression in pwALS/MS31; and one cohort study of Coping Effectiveness Training in pwALS and/or their caregivers was withdrawn prior to enrolment32. Another RCT is reportedly underway of a meditation training program modified for pwALS/carers33, although details are unknown as it has not been registered on any clinical trial database.

Of the five studies identified, two adopted a RCT design (both with a maximum follow-up interval of 6 months)24,30, one adopted a CT design28 and two adopted a cohort design (pre- vs. post-)26-27,29. The majority of studies recruited participants from outpatient clinics, with one study recruiting from both the community and outpatient clinics24 and one study recruiting from just the community26-27. No study included participants where they were selected for the presence of significant depression/anxiety/distress, with the exception of one which required that participants score in the clinical range on a mood questionnaire in order to be randomly allocated to a psychotherapy condition30. The type of psychotherapeutic intervention differed in all studies (two articles reported data from the same participant sample26-27), and all but one involved face-to-face therapist contact. A non-active control condition was used in three studies24,28,30, while two lacked a control condition26-27,29 and no studies employed an active control condition. The number of participants ranged from 8 to 54 in the completed studies24,26-29, while the anticipated number for the ongoing study was 40 per condition30. In the completed studies, participants were typically middle-aged to older men who had received a diagnosis of ALS within the previous 3 years.

**Study findings**

The only psychotherapy RCT completed to date involved self-help expressive disclosure (i.e. facilitation of emotional expression) in which participants were required to write or talk about their deepest thoughts and feelings in relation to their experience of ALS during a 1-week period24. Participants in the disclosure condition reported significantly higher levels of wellbeing than those in the no-disclosure condition at 3- but not 6-months post-intervention, although this effect was moderated by ambivalence over emotional expression. The authors did not examine wellbeing immediately after the intervention and so the immediate short- and longer-term effects (beyond 6 months) are unknown. A non-randomised CT comparing CBT combined with counselling techniques with pharmacotherapy reported significant pre-post differences in depression and anxiety in the intervention but not control group28. However, significant between-group differences in anxiety and time since diagnosis were found at baseline and not subsequently controlled for. In addition, the longer-term effects of the intervention are unknown as there was no follow-up.

Two pre-post cohort studies have been completed to date: one evaluated dignity therapy26-27 and one evaluated a hypnosis-based intervention29. Dignity therapy comprised a brief life review intervention in which pwALS were encouraged to reflect on significant memories, events and accomplishments in their life. No significant pre-post differences in levels of hopefulness, dignity or spiritual wellbeing were observed; an unsurprising result given that high levels of hopefulness, low levels of dignity-related distress and moderate levels of spiritual wellbeing were reported at baseline. The hypnosis-based intervention involved hypnotic suggestion with guided visual imagery, together with training in self-hypnosis. Significant pre-post decreases in depression, anxiety, and some aspects of quality of life were reported. Again, the longer-term effects of dignity and hypnosis-based therapy are unknown as there was no follow-up in these studies.

Results are currently awaited for one further study: a multi-centre RCT of exercise therapy vs. CBT vs. usual care30. In this study, CBT will address ALS-specific issues (e.g. coming to terms with the diagnosis, coping with mood issues, and maintaining autonomy, activities and relationships), and will be delivered in a modular format, with the choice of modules being individually tailored to pwALS and their caregivers. Similar to previous studies, although this study will be able to inform about the shorter-term effects of psychotherapy (up to 6 months), the longer-term effects remain unexplored. Further details about the results of these studies are highlighted in Supplementary Table 1.

**Quality assessment and critical appraisal**

As shown in Table 2, the quality of completed studies was variable but generally poor, with risk of bias only being adequately addressed in 1-2 areas. Incomplete outcome data was the area most adequately addressed, while blinding of participants was least adequately addressed. No study included an adequate placebo that ensured participants could be blinded to the research question, and only one study reported blinding of outcome assessors30. A truly random sequence generation was used in only one study24, and allocation concealment was unclear in the majority of studies. There was evidence of selective outcome reporting in one study24.

A number of potential sources of patient heterogeneity and factors that may confound or influence the interpretation or generalisability of results were also identified (see Table 3). With respect to patient heterogeneity, one study did not report using revised El Escorial criteria for diagnosing ALS26-27 and two studies did not report site of ALS onset (limb/spinal vs. bulbar)24,26-27, and so the variability in presentations across studies, and subsequent impact on results, is unknown. Distress or wellbeing was not specified as an inclusion criterion in four studies24,26-27,29 (but was implied in one study where antidepressant use was an inclusion criterion24), and so it is unclear how many participants were experiencing significant depression/anxiety/distress. This may have impacted on results as intervention trials that include non-distressed patients are less likely to show beneficial effects.

Turning to other factors that may confound or influence the interpretation of results, four studies completed screening of cognitive abilities24,26-27,29-30, though details were frequently lacking. However, the exclusion criterion for cognitive impairment in two studies meant that some participants may have been experiencing mild-to-moderate cognitive impairment (as in fact noted in one study)24,26-27. Concurrent psychotherapy or pharmacotherapy were permitted in three studies24,26-27, and so the extent to which this may have impacted on results is uncertain, especially since these variables were not controlled for in statistical analyses. With respect to treatment fidelity, no study reported using a therapy manual and only one employed therapist adherence checks26-27. Furthermore, no study employed an active control condition. Consequently, the extent to which beneficial effects were attributable to the prescribed psychotherapy, additional therapeutic components introduced due to lack of treatment fidelity, or non-specific therapeutic factors (e.g. therapist attention and social support) is unclear. In addition, the extent to which beneficial effects may have been attributable to potential antidepressant effects of riluzole34-35 was also uncertain given that no studies reported on its use. Finally, generalisability of results was limited in two studies in which self-referrals were permitted24,26-27 since those self-referring may not be representative of the ALS population.

**DISCUSSION**

The aims of this review were to systematically and critically evaluate the effectiveness of psychotherapy and pharmacotherapy interventions for reducing distress or improving wellbeing in pwALS. Five studies of psychotherapy and no studies of pharmacotherapy were identified. Improvements in wellbeing were reported in three out of four completed studies in the short-term only, but were not investigated beyond 6 months follow-up. The quality of the completed studies was relatively poor, as all were at risk of bias in a number of areas. However, it should be stressed that this is an issue common to other reviews of psychotherapy interventions rather than being specific to studies in pwALS36-37. Furthermore, sample sizes were small (overall N=145), which may be a reflection of the challenges that come with recruiting participants with ALS into research studies (e.g. the prevalence of ALS, the typical survival rate and tolerability to engaging in such studies). In addition, there was considerable heterogeneity in the interventions, outcome measures and study designs used, as well as the clinical presentation of participants. Consequently, at present, there is insufficient evidence to support the use of specific psychotherapy interventions for reducing distress or improving wellbeing in pwALS. This is despite a previous call for research on the efficacy of psychological interventions in this population22. Moreover, there is a lack of evidence for pharmacotherapy interventions at this time. Neither of these findings should be interpreted as proof of ineffectiveness, but instead highlight the significant gaps that exist in the current literature.

**Clinical recommendations**

Although previous authors3,21-22,38 have suggested the use of a variety of pharmacotherapies and/or psychotherapies for reducing distress or improving wellbeing in pwALS, no specific evidence-based clinical recommendations can be made at this time. Suggestions from clinical practice have generally been based on what is known to be effective in working-age and older adult populations with mood disorders, but can also be drawn from existing literature on psychotherapy interventions for those with progressive degenerative neuromuscular disorders. For example, while the evidence base is relatively small, a recent review notes the potential importance of Acceptance and Commitment Therapy in such populations, given the potential role of acceptance as a mediating factor in the relationship between disease symptomatology and quality of life39.

**Research recommendations**

There is a pressing need to examine pharmacotherapy and psychotherapy interventions within high quality, multi-site, double-blind RCTs, both in the short- and longer-term, before any strong conclusions can be drawn about their effectiveness in pwALS. Clarifying these points further, multi-site RCTs of pharmacotherapy and psychotherapy interventions may be one way of improving sample sizes given the challenges noted above of recruiting pwALS into intervention studies. Although blinding of participants in psychotherapy RCTs is difficult, it is not impossible, as illustrated in previous studies that have employed adequate 'talking controls' for psychotherapy interventions40-41. Finally, it is important to assess outcomes in the longer-term, as well as the shorter-term, as any gains in wellbeing may be short-lived given the rapidly progressive nature of ALS.

With respect to specific recommendations for pharmacotherapy interventions, as previous reviews have suggested the use of citalopram, venlafaxine, amitriptyline, nortriptyline or mirtazapine for depression, and bupropion, diazepam, lorazepam or midazolam for anxiety21,38,42, examining these would be an obvious place to start. Studies of psychotherapy interventions could evaluate the effectiveness of interventions such as CBT or mindfulness-based therapy, modified to meet the needs of pwALS, as suggested previously3,33. Such studies could also assess the benefits of including caregivers in the interventions given that this may not only help improve their wellbeing, but also that of the cared-for person43-44. In addition, such studies could focus on the alleviation of distress and its prevention in order to reduce unnecessary suffering caused by depression or anxiety. Finally, studies could explore whether a combination of pharmacotherapy and psychotherapy can produce superior outcomes to either approach alone, and whether bio-psychosocial factors (e.g. site of ALS onset, co-morbid cognitive impairment, and therapeutic modifications to account for physical/communication deficits) moderate the effectiveness of these approaches.

**Strengths and limitations**

To the authors’ knowledge, this systematic review is the first to examine psychotherapy interventions for reducing distress or improving wellbeing in pwALS, and represents an update to previous reviews of pharmacotherapy in this population. A limitation is that a meta-analysis could not be conducted due to the small number of identified studies and heterogeneity in clinical and research variables. A further limitation is that a partial rather than comprehensive search of grey literature was completed, and so this review may be subject to some publication bias. For example, authors/experts in the field were not contacted about unpublished data, and other grey literature sources45 were not searched. A more comprehensive search may have identified more studies, though this may have introduced further bias as it has been noted that difficult-to-locate studies are often of lower methodological quality46.

**Conclusions**

There is currently insufficient evidence to support the use of specific psychotherapy interventions for reducing distress or improving wellbeing in pwALS, and no evidence for pharmacotherapy. In the absence of such evidence it is tempting to extrapolate findings from intervention studies in non-ALS populations to those with ALS. However, this should not be presumed as numerous factors may moderate the effectiveness of pharmacotherapy and/or psychotherapy in pwALS. Consequently, further research is urgently needed to examine how distress can be alleviated, how gains in distress reduction can be maintained, and how distress can be prevented or wellbeing can be enhanced in those living with the devastating consequences of ALS.

**ACKNOWLEDGEMENTS**

RLG and RJH receive salary support from King’s College London and the South London and Maudsley NHS Foundation Trust. MCC receives salary support from Middlesex University. RGB, LHG and AAC receive salary support from the NIHR Dementia Biomedical Research Unit and/or the NIHR Biomedical Research Centre for Mental Health, both at King’s College London and the South London and Maudsley NHS Foundation Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The authors would like to express their gratitude and thanks to all those authors who responded to queries about their studies, and to two anonymous reviewers for their helpful comments.

**DISCLOSURE OF INTERESTS**

None

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**Legends of Tables and Figures**

Table 1: Characteristics of studies included in the systematic review.

Table 2: Potential sources of bias in studies included in the systematic review.

Table 3: Further critical appraisal of studies included in the systematic review.

Supplementary Table 1: Results of studies included in the systematic review.

Figure 1: Flow of studies in the systematic review.

Table 1: Characteristics of studies included in the systematic review.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study reference** | **Type of study** | **Status** | **Referral setting** | **Inclusion criteria** | **Exclusion criteria** | **Mean years since ALS diagnosis** | **Tx****Other comparator** | **Control (type)** | **Number of sessions (duration)** | **Mode of Tx** | **No. Tx Ps** | **No. control Ps** | **Mean age (range)** | **% male** |
| 24 | RCT | Completed | Outpatient clinic & community | Diagnosis of definite or probable ALS >=6 months ago; >18 years old; >=50% FVC | Significant dysfunction on COWAT | 2.4 | Verbal or written expressive disclosurea | No disclosure (non-active) | 3 over 1 week (20 minutes) | NA1 | 27 | 27 | 60.2 (40-81) | 68.8 |
| 25-27b | Cohort | Completed | Community | Diagnosis of MND; >18 years old; English speaking; able to provide informed consent; below cut-off score of 10 on ALS-CBS or <15 on BOMCT | Too ill to complete the study | NS (N=21 <=3, N=8 >4)N=20 <=3, N=7 >4 | Dignity Therapy | NA | 3-7 over a mean completion time of 42 days (NS)3-7 over a median completion time of 36 days (mean 2 hrs) | Individual or with caregiver | 29c27c | NA | NS: N=6 <60, N=23 >=60 (32-81)64.3 (32-81) | 69.066.7 |
| 28 | CT | Completed | Outpatient clinic | Diagnosis of definite or probable ALS; clinically stable; managed by a respiratory care unit | Previous pulmonary disease; dementia; no psycho-active drug treatment | 3.2 | CBT with counselling techniques | Psycho-active drug treatment | 4 (1 hour) | Individual plus family and family alone | 30 | 24 | 63.1 (NS) | 29.6 |
| 29 | Cohort | Completed | Outpatient clinic | Diagnosis of definite or probable ALS | NS | 1.7 | Hypnosis-based intervention | NA | 4 over 4 weeks (45 minutes) | Individual | 8 | NA | 56.1 (NS) | 50.0 |
| 30 | RCT | Ongoing | Outpatient clinic | 18-70 years old; >1 year life expectancy; >=80% FVC; diagnosis of definite or probable ALS >=1 month ago; in rehabilitation phase; walking & cycling ability | Cognitive impairment; insufficient mastery of Dutch; disabling co-morbidity (e.g. cardio-pulmonary disease, diabetes, etc); psychological disorder preventing Tx completion | NYK | CBT & TAUAET & TAU | TAU alone (non-active) | CBT: 5-10 over 16 weeks (60 minutes)AET: 3x per week for 16 weeks (max. 35 minutes at home, max. 60 minutes in clinic) | CBT: Individual or with partnerAET: Individual & group | NYKd | NYKd | NYK (18-70) | NYK |

*Notes:* aNo therapist involvement; bboth studies report data from the same participant sample (26 is the original publication and 27 is the subsequent publication); ca smaller N is given in 27 compared to 26 as the former study only reported data for participants who were registered with the MND Association of Western Australia, as confirmed in personal communication with the authors, and so characteristics are reported for both studies where differences exist due to this variation; dplanning to recruit N = 40 per condition; AET = aerobic exercise therapy; ALSCBS = ALS-Cognitive Behavioural Screen; BOMCT = Blessed Orientation Memory Concentration Test; CBT = Cognitive Behavioural Therapy; CT = controlled trial; COWAT = Controlled Oral Word Association Test; FVC = forced vital capacity; NA = not applicable; NS = not specified; NYK = not yet known; post-rand = post-randomisation; Ps = participants; RCT = randomised controlled trial; TAU = treatment as usual; Tx = treatment.

Table 2: Potential sources of bias in studies included in the systematic review.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study reference** | **Type of study (type of control)** | **Cochrane Collaboration Risk of Bias Tool** | **No. of adequate ratings** | **Further information** |
| **Randomisation: Sequence generation** | **Randomisation: Allocation concealment** | **Blinding of participants** | **Blinding of outcome assessors** | **Incomplete outcome data** | **Selective outcome reporting** |
| 24 | RCT (non-active) | Adequate | Unclear | Inadequate | Unclear | Adequate | Inadequate | 2/6 | No adequate placebo control; no information provided about allocation concealment or blinding of outcome assessors; immediate post-intervention data excluded from majority of analyses; group x time interaction but not main effects of group and time reported. |
| 25-27a | Cohort (none) | Inadequate | Inadequate | Inadequate | Unclear | Adequate | Adequate | 2/6 | No adequate placebo control; no randomisation; no information provided about blinding of outcome assessors. |
| 28 | CT (non-random) | Inadequate | Inadequate | Inadequate | Unclear | Adequate | Adequate | 2/6 | No adequate placebo control; no randomisation; no information provided about blinding of outcome assessors. |
| 29 | Cohort (none) | Inadequate | Inadequate | Inadequate | Unclear | Adequate | Adequate | 2/6 | No adequate placebo control; no randomisation; no information provided about blinding of outcome assessors. |
| 30 | RCT (non-active) | Inadequate | Adequate | Inadequate | Adequate | Not yet known | Not yet known | 2/4 | No adequate placebo control; quasi-random allocation (patients who exercise 2+ hours per week & score <8 on HADS can only be allocated to TAU). |

*Notes:* aBoth studies report data from the same participant sample (see Table 1 for further explanation); CT = controlled trial; RCT = randomised controlled trial.

Table 3: Further critical appraisal of studies included in the systematic review.

|  |  |  |  |
| --- | --- | --- | --- |
| **Study reference** | **Potential sources of patient heterogeneity** | **Factors that may confound or influence the interpretation or generalisability of results** | **Additional comments** |
| **Definite or probable ALS using REE criteria (no. bulbar/ LS/mixed onset)** | **Inclusion criterion for psychological distress or wellbeing** | **Screening of cognitive abilities** | **No. receiving concurrent psychotherapy** | **No. receiving concurrent pharmacotherapy with AD or AX** | **Manualised therapy/****therapist adherence checks** | **Non-specific therapeutic effects controlled for** | **No. receiving riluzole** | **Self-referral allowed** |
| 24 | Yes (NK/NK/NK) | None | Yes (significant dysfunction on COWAT) | 9/48 | 16/48 AD, NS AX | NAa / NAa | No | NK | Yes | Some may have been experiencing mild to moderate cognitive impairment; fairly small sample size. |
| 25-27b | No (NK/NK/NK)cNo (11/NK/NK)c | None | Yes (cut-off score of 10 on ALSCBS or 9 on BOMCT)cYes (cut-off score of 15 on BOMCT)c | NS | 7/29 AD, 3/29 AXcNSc | NS / Yes | No | NK | Yes | Suspected mild to moderate cognitive impairment in 10/29 (reported in Bentley et al. but not Aoun et al.); fairly small sample size; duplicative data reportingb. |
| 28 | Yes (19/35/0) | None | None | NS | 54/54 AD or AX | NS / NS | No | NK | No | Allocation to intervention or control group based on ability to attend hospital; different length of time between Pre and Post assessments in the intervention and control groups; between-group differences at Pre (higher anxiety in intervention vs. control group and longer time since diagnosis in control vs. intervention group) not controlled for; fairly small sample size. |
| 29 | Yes (2/6/0) | None | Yes (NS) | NS | NS | NS / NS | No | NK | No | No changes in neuropsychological profiles reported; very small sample size. |
| 30 | Yes (NYK/NYK/ NYK) | Score of >=8 on HADS for CBT arm | NS ("cognitive impairment") | NYK (allowed as part of TAU) | NYK | NS / NS | No | NYK | No | Excluding those with a psychological disorder that may prevent completion of the intervention; planning to recruit fairly small sample. |

*Notes:* aNo therapist involvement; bboth studies report data from the same participant sample (see Table 1 for further explanation); cinformation is reported for both studies where between-study differences exist in reporting; AD = antidepressants; ALSCBS = ALS-Cognitive Behavioural Screen; AX = anxiolytics; BOMCT = Blessed Orientation Memory Concentration Test; CBT = Cognitive Behavioural Therapy; COWAT = Controlled Oral Word Association Test; HADS = Hospital Anxiety and Depression Scale; LS = limb or spinal; NA = not applicable; NK = not known; NYK = not yet known; NS = not specified; Pre = Pre-intervention; Post = Post-intervention; pwALS = people with ALS; REE criteria = Revised El Escorial criteria.