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REVIEW ARTICLE

Prevalence of pain in amyotrophic lateral sclerosis: a systematic review and meta-analysis

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Abstract

Objectives: Physical pain is a known symptom in amyotrophic lateral sclerosis (ALS), but no systematically derived prevalence estimate is available. The aim of this study was to determine the pooled prevalence of pain in ALS, relative to its method of measurement and pain characteristics. *Methods*: A systematic search across multiple databases was conducted on January 16, 2020. Random-effects meta-analyses of single proportions were performed on prevalence data. Heterogeneity was determined using the I^2 statistic. Where available, pain location, intensity, and type or source were compared. *Results:* 2552 articles were identified. Twenty-one eligible studies were included. All studies used observational designs (14 cross-sectional, 6 cohort, 1 case-control). Pooled prevalence of pain in ALS across all studies was 60% (95% CI = 50–69%), with a high degree of heterogeneity (I^2 = 94%, p < .001). Studies that used only validated measures had lower heterogeneity (I^2 = 82%, p = 0.002), compared to those that used tailored measures, or tailored supplemented with validated measures (I^2 = 90%, p < 0.001 and I^2 = 83%, p < 0.001, respectively). In a subset of studies (N = 9), the most commonly reported pain location was the upper limbs including shoulders/extremities (41.5%). A further study subset (N = 7) showed moderate-severe intensity pain was most frequently reported. Type of pain was commonly related to cramp or spasm. *Conclusions:* Experiencing physical pain in ALS occurs with high prevalence. Deriving consensus on which specific tools should be used to assess, monitor and compare symptoms of pain in this population will reduce current heterogeneity in approaches and increase the likelihood of ameliorating distressing experiences more effectively.

keywords: *Pain, amyotrophic lateral sclerosis, motor neurone disease, meta-analysis*

Introduction

Pain is an important and common symptom in patients with amyotrophic lateral sclerosis (ALS) (1–3). It has many causes; it is likely that more than one type may occur in any individual. Types of pain include: muscle cramp, neuropathic pain, joint pain, muscle and fibrous tissue pain, or pain from intervertebral disk protrusion or spondylosis exacerbated by or associated with postural disturbance (2,4). In the UK, the National Institute for Health and Care Excellence (NICE) guidelines do not address the issue of pain in ALS management (5) as there is limited research on the effectiveness of treatment (6,7). In ALS, research has shown that pain can impact on an individual's life across physical, psychological, social, and spiritual domains (3). It is an important symptom requiring palliation within specialist multidisciplinary ALS care (8).

Studies estimating prevalence of pain in ALS have produced a wide range of results suggesting rates as low as 15% to as high as 85% (2,4). While reviews have been conducted in the area of pain in

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ALS (e.g., (2,4)), there are currently no systematic reviews or meta-analyses to determine specifically the prevalence of pain, its detection, and associated features in ALS. Previous research suggested that improvements are needed to standardize assessments to help target pain management practices (9). A more thorough understanding, measurement, and quantification of pain in ALS is needed to improve clinical practice.

The primary aim of this study was to systematically determine the pooled prevalence of pain in ALS. The secondary aims were to explore the common evaluation characteristics of pain (such as location, intensity, and type of pain), and account for the type of methods used in measuring pain in ALS.

Methods

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines (10).

Search strategy and eligibility criteria

The searches included both medical subject headings (MeSH) and keyword terms (with spelling variants), for the condition of ALS ("Amyotrophic Lateral Sclerosis" OR "Motor Neurone Disease" OR "Motor Neuron Disease" OR "Lou Gehrig's Disease") AND the symptom of pain ("Pain"). Eligibility criteria were primary research studies or secondary data analysis that included pain prevalence data for people with a diagnosis of ALS above the age of 18. Exclusion criteria were case-studies, editorials and letters to the editor, grey literature, and conference proceedings. Searches were restricted to the English language.

Information sources

The following databases were searched systematically from inception to 1st February 2019: MEDLINE and Embase via OVID, Cochrane CENTRAL, CINAHL, AMED, PsycINFO, and Scopus. Scopus was used as a citation tracking tool to supplement database searches. The searches were updated on 16th January 2020 using the same databases.

Study selection and data extraction

In Stage 1, the search strategy was codesigned by all authors. The initial database searches were performed by author N.H., and duplicate results were removed. In Stage 2, a reviewer (author N. H.) screened titles and abstracts to determine article eligibility and applying exclusion criteria for the full-text review (Stage 3). Any articles marked as uncertain for inclusion in Stage 2 were automatically progressed for full article screening (Stage 3) using the eligibility and exclusion criteria. Stage 3 (full article review) was conducted by the same reviewer (author N. H.). Any full-text articles marked as uncertain for inclusion were reviewed by 2 additional members of the review team (authors R. R. and G. P.) until consensus was determined. All final papers were additionally reviewed (author R. R.) before final inclusion.

Data extracted from full-text articles included the study design, sample size, sample source, pain assessment method, male/female ratio, average age, and pain prevalence estimate. Where available, data on location of pain, type of pain, and its intensity were extracted. For longitudinal studies, only baseline data was extracted in order to standardize prevalence comparisons.

Quality assessment

All included full-text articles were assessed for quality by one reviewer (N. H.) and moderated by an additional reviewer (R. R.) using either the Appraisal Tool for Cross-sectional Studies (AXIS) (11) or the Critical Appraisal Skills Programme (CASP) Study checklist (12).

Statistical analyses

Extracted data and quality assessment ratings underwent descriptive comparison. The meta package within R Software (13) was used for random-effects meta-analysis of single proportions for prevalence estimates, and to create forest plots of the data (14). The Cochranes Q (χ^2) test and I^2 statistic was used to estimate what percentage of the variation across studies is due to heterogeneity rather than chance. An I^2 value of $>75\%$ suggests considerable heterogeneity (15). 95% confidence intervals (CI) were calculated alongside the prevalence of pain statistic (16). An additional exploratory subgroup analysis of the types of pain measures used was performed. Measures were classified as either validated (e.g., structured scales/measures/questionnaires), tailored (e.g., interviews/single questions/multiple questions), or tailored supplemented with validated measures.

Where available, data were pooled to describe the total number of participants per location of pain and re-classified into three specific data-driven regional categories: head/neck/trunk/back, upper limbs including shoulders/extremities, and lower limbs including extremities. Upper limb extremities included fingers and hands, and lower limb extremities included toes and feet. In ambiguous cases where the location of pain was uncertain or distributed across multiple regions (i.e., "upper/lower limbs"), these were allocated to all relevant location categories to ensure inclusivity and avoid underestimation for specific locations. The proportion for each specific region was calculated by summing the number of individuals reporting the specific pain locations (i.e., head/neck/trunk/back)

and dividing it by the sum of all individuals reporting pain locations over all studies, multiplied by 100. This produced a percentage per region. The formula is presented below:

$$\left(\frac{\sum(N\ of\ \text{Specific Pain Location})}{\sum(N\ of\ \text{All Pain Locations})}\right) \times 100 = \%\ \text{Pain in Specific Region}$$

Where reported, pain intensity data were extracted and reclassified into "mild", "moderate", "severe", and "very severe" intensity categories where necessary. Percentages were calculated for each category using this formula:

$$\left(\frac{\sum(N\ of\ \text{Specific Pain Intensity Category})}{\sum(N\ of\ \text{All Pain Intensity Categories})}\right) \times 100 = \%\ \textit{S}\text{pecific Pain Intensity Category}$$

Results

Search results

Figure 1 shows the full screening process. The initial and updated searches identified 2552 articles, with 172 full-text articles screened for eligibility, where less than 5% of those were reviewed by add-

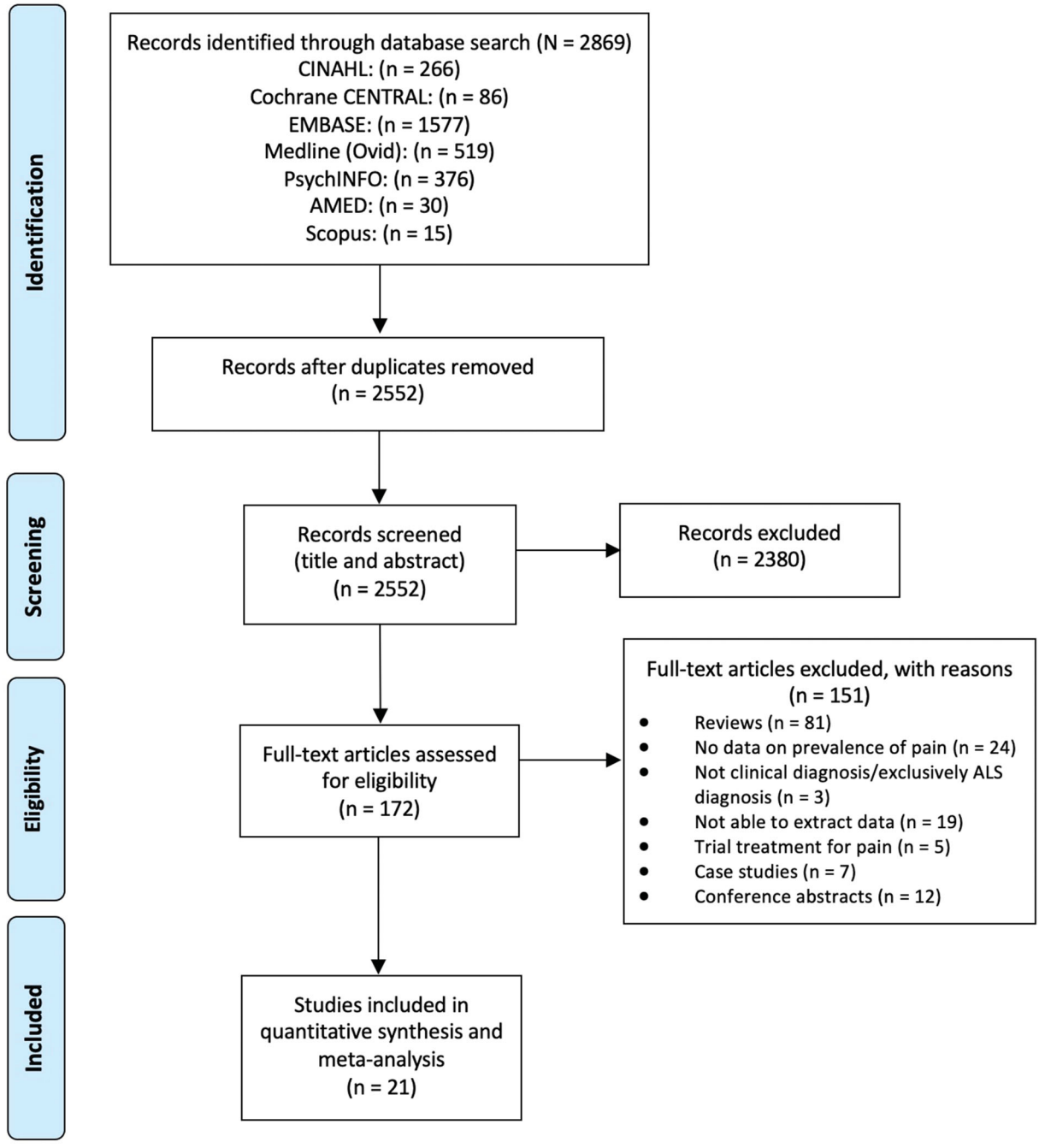

Figure 1. Prisma Flowchart (10).

Table 1. Summary of all included studies ($N = 21$).

Study	Design	Sample source (site and country)	Sample size	Pain assessment method	Sex M/F (N)	Average age (years)	Pain prevalence estimate (%)	95% Confidence intervals (%)
Abe et al. (17)	Cross-sectional	Outpatients at the University of Tokyo Hospital, Japan	7	Face-to-face Interview, presence/absence (supplemented by BPI)	—	—	57.1	20.4–93.8
Caress et al. (18)	Cohort	Wake Forest ALS Center, Winston-Salem, NC, USA	41	Telephone or face-to-face interviews	23/18	64.0	78.0	65.9–90.7
Chiò et al. (19)	Population-based case-control (Cohort)	ALS patients with residence in Torino, Italy via the Piemonte and Valle d'Aosta register for ALS	160	BPI	91/69	62.4	56.9	49.2–64.6
Ganzini et al. (20)	Cross-sectional	ALS Clinic at Oregon Health Sciences University in Portland, Oregon, USA	100	6 Likert point scale, single item rating	61/39	54.0	56.0	46.3–65.7
Hanisch et al. (21)	Cross-sectional	ALS and Motor neurone disease outpatient clinic at Martin-Luther-University, Halle, Germany	46	BPI	20/26	64.0	78.3	66.4–90.2
Ho et al. (22)	Cohort	Lahey Clinic Medical Center, Burlington, Massachusetts, USA	193	Retrospective Medical Record Review	97/96	63.0	23.3	17.3–29.3
Ishida et al. (23)	Cross-sectional	Eight hospitals that are members of Tokai Hokuriku National Hospital Pharmacists Association in Japan	80	Questionnaire using the WBS	45/35	65.0	53.8	42.9–64.7
Jensen et al. (24)	Cross-sectional	Neuromuscular disease (NMD) rehabilitation clinic, University of Washington Medical Center. NMD clinic, research and training center, University of California, USA	30	Questionnaire, presence/absence (supplemented by mixed items taken from the GCPS, NPS, SF-MPQ, BPI)	—	—	60.0	42.5–77.5
Kehyayan et al. (25)	Cross-sectional	The Complex Continuing Care Reporting System and the Ontario Association of Community Care Access Centers database, Canada	2092	PS	—	—	61.2	59.1–63.3
Moisset et al. (26)	Cross-sectional	ALS Center at Clermont-Ferrand University Hospital, Auvergne, France	93	DN4 questionnaire	57/36	—	65.5	55.8–72.3
Ng et al. (27)	Cross-sectional	Tertiary Motor Neurone Disease multidisciplinary clinic that services Victoria, Australia	44	Interviews with open-ended questionnaire and self-administered questionnaire	29/15	60.9	50.0	35.2–64.8
Pagnini et al. (28)	Cohort	Neuromuscular Omnicentre in Milan, Italy	40	QUID	—	—	47.5	32.0–63.0

(*Continued*)

Table 1. (*Continued*).

Study	Design	Sample source (site and country)	Sample size	Pain assessment method	Sex M/F (N)	Average age (years)	Pain prevalence estimate (%)	95% Confidence intervals (%)
Pizzimenti et al. (29)	Cross-sectional	Multidisciplinary outpatients ALS center at the Sapienza University of Rome, Italy	36	Clinical assessment (supplemented by NPSI)	22/14	63.7	72.2	57.6–86.8
Rivera et al. (30)	Cross-sectional	Clinic, Chicago, USA	64	NPS and body cartoon	40/24	57 (Median)	51.6	39.4–63.8
Sandstedt et al. (31)	Cohort	ALS clinic at the Karolinska University Hospital, Stockholm, Sweden	60	Questionnaire, presence/absence (supplemented by Numeric rating scale for severity)	32/28	61 (Median)	66.7	46.5–86.9
Stephens et al. (32)	Cross-sectional	Agency for Toxic Substances and Disease Registry, National ALS Registry, USA	287	PROMIS Questionnaire	184/103	58.0	92.0	88.9–95.1
Taga et al. (33)	Cross-sectional	Motor Neuron Diseases Center, Parma, Italy	108	Retrospective Medical Record Review	55/53	—	19.4	12.0–26.9
Tiirola et al. (34)	Cohort	Pirkanmaa Hospice, Finland	32	Retrospective Medical Record Review	8/24	69.0	46.9	29.6–64.2
Trail et al. (35)	Cross-sectional	ALS clinic at the Baylor College of Medicine, Houston, USA	27	Questionnaire (internally generated single-item attitude scale)	18/9	57.2	33.3	15.5–51.1
Wallace et al. (36)	Case-control	Specialist Multidisciplinary clinic, UK	24[a]	BPI, painDetect questionnaire	17/7[a]	57.3[a]	85.7[a]	74.3–100.0
Winter et al. (37)	Cross-sectional	Seven specialized centers of the German Network of Muscle Disorders, Germany	37	EQ-5D	21/16	59.6	75.7	61.9–89.5

A dash (-) indicates where data was not available. Average age is mean, unless otherwise stated.

BPI: Brief Pain Inventory; DN4: The Douleur Neuropathique–4 [Neuropathic Pain Diagnostic Questionnaire]; EQ-5D: Euroqual Instrument; GCPS: Graded Chronic Pain Scale; M/F: Male to Female ratio; N: number of people; NPSI: Neuropathic Pain Symptom Inventory; NPS: Neuropathic Pain Scale; PROMIS: Patient Reported Outcome Measurement Information System; PS: Pain Scale; QUID: [Italian Pain Questionnaire]; SF-MPQ: Short-Form McGill Pain Questionnaire; WBS: Wong-Baker Faces Pain Rating Scale.

[a]Only those with a diagnosis label of "ALS".

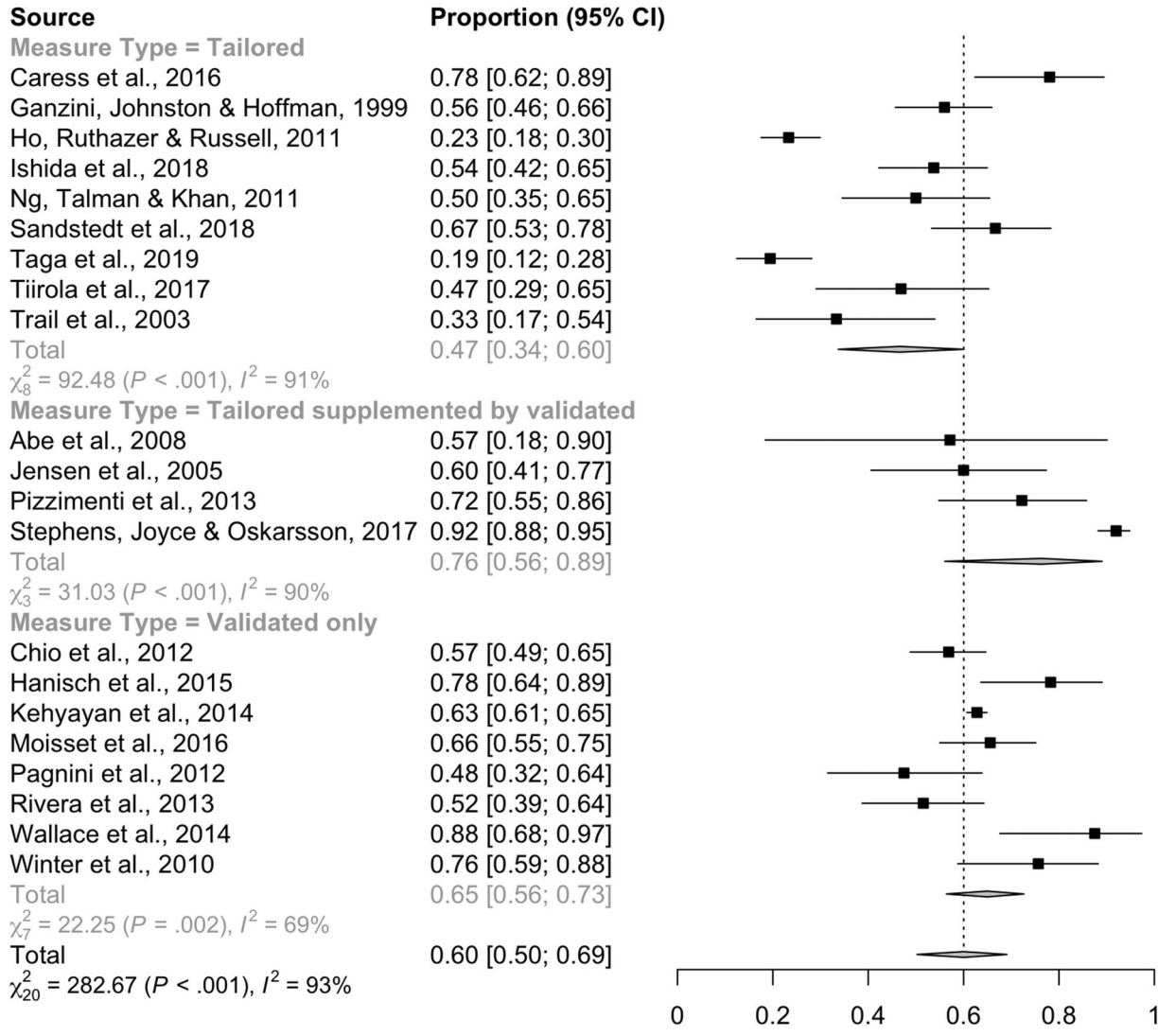

Figure 2. Forest Plot of pooled prevalence of pain in ALS across all studies ($N = 21$), including pooled prevalence subdivided by measure type.

itional team members for inclusion. Twenty-one studies were found to meet the inclusion criteria (17–37). Table 1 shows summary details of all included studies. Of the 21 studies included, all were observational studies; 14 used a cross-sectional design (17,20,21,23–27,29,30,32,33,35,37), six used a cohort design (18,19,22,28,31,34) and one case control study (36). The studies yielded a total of 3601 ALS patients with study sample sizes ranging from 7 to 2092 participants with the median sample size of 46 (inter quartile range = 64). There was an overall heterogeneity of pain assessment methods, including validated questionnaires, combinations of questions from validated scales, retrospective medical record review, and single-item questions (both with and without additional validated measures). The most commonly used validated measure used was the Brief Pain Inventory (BPI) but this was only in $N = 4$ of the included studies.

Summary of quality assessment

Overall, the eligible studies were of adequate quality, with clear aims/objectives, descriptions of study populations, and justifiable results and findings. Issues emerged regarding justification of sample size, measurement of confounds, use of valid, and standardized outcome measures (of pain), methodological clarity, and follow-up with participants. Quality ratings for all included studies can be found in Supplementary Table 1.

Prevalence of pain

All included studies ($N = 21$) provided data for the prevalence of pain in ALS. Figure 2 presents a forest plot of all nineteen articles included in the meta-analysis, illustrating the substantial heterogeneity of overall results ($I^2 = 94\%$, $p < 0.001$). The overall pooled pain prevalence across all included studies was 60% (95% CI = 50–69%),

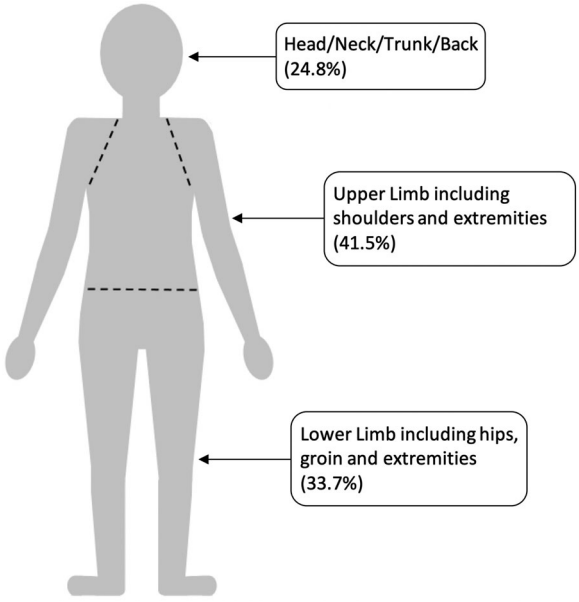

Figure 3. Locations of pain in subgroup of ALS pain studies ($N = 9$).

suggesting that between half and two-thirds of all ALS patients experience pain. Table 1 shows the individual study data for pain prevalence ranged from 19.4 to 92.0%. Smaller sample sizes present larger confidence intervals indicating lower precision. Larger samples produce more reliable results. Notably, Kehyayan et al. (25) produced a prevalence estimate close to the overall pooled pain prevalence across all studies (represented by the vertical dashed line in Figure 2); this study had the largest sample size ($N = 2092$).

Figure 2 displays the subgroup analysis with studies divided according to pain measure type. Tailored measures for determining the prevalence of pain in ALS were used in nine of the included studies (18,20,22,23,27,31,33–35). Eight studies used validated measures only (19,21,25,26, 28,30,36,37). Four studies used tailored measures of pain supplemented by validated measures (17,24,29,32). Both tailored measures and tailored supplemented by validated measures showed considerable heterogeneity ($I^2 = 90\%$, $p < 0.001$ and $I^2 = 83\%$, $p < 0.001$, respectively). There was a larger disparity in pooled pain prevalence between tailored measures, 47% (95% CI = 34–60%), and tailored supplemented by validated measures, 76% (95% CI = 56–89%). Only validated measures showed a lower degree of heterogeneity ($I^2 = 82\%$, $p = 0.002$), but still relatively high. The pooled pain prevalence of 65% (95% CI = 56–73%) of only validated measures was closest to that of the overall pooled pain prevalence across all studies of 60% (95% CI = 50–69%).

Pain location

The location of pain was addressed in nine of the included studies (19–23,26,29,30,33). A total of 393 participants reported 715 locations of pain (see Supplementary Table 2 for details). Figure 3 shows location categories of pain from the nine included studies. The most commonly reported pain location was the upper limbs including shoulders/extremities, followed by lower limbs including extremities. Reports of pain in the head/neck/trunk/back were lowest.

Pain characteristics

Intensity of pain was reported in seven of the included studies by a total of 1426 participants (18,19,21,24,25,28,29). However, data provided were incomplete, with "severe pain" being reported consistently across studies. From the total number of participants reporting pain intensity ($N = 1426$), moderate ratings were reported most (78.8%, $N = 1124$), followed by severe ratings (17.5%, $N = 250$). Mild and very severe intensity pain were reported least (2.0%, $N = 28$ and 1.7%, $N = 24$, respectively). In a more detailed examination, four of the studies (18,24,25,28) found the majority of participants reported moderate pain, ranging from 33.0% ($N = 6$) to 51.5% ($N = 1077$). One study reported severe pain intensity at 13.8% ($N = 22$) with no other pain categories listed (19) and one other study showed that 65.4% ($N = 17$) of participants experienced very severe pain (29). Contrastingly, Hanisch et al. (21) found the greatest proportion of participants reported mild pain at 58.0% ($N = 21$), with 39.0% ($N = 14$) having moderate pain. See Supplementary Table 3 for specific breakdown and details of pain intensity.

Specific types or source of pain were reported in seven of the included studies (18,21,26,27,30,32,33). Cramps and spasms were the most commonly reported types of pain in six of the included studies (18,21,27,30,32,33). Two studies (18,32) directly examined muscular cramps as the source of pain, and therefore 100% ($N = 264$ and $N = 32$, respectively) of the pain reported in these studies was related to cramps. A further two studies (21,33) also included cramps in their study. They reported that 63% ($N = 29$) and 37.5% ($N = 6$) of individuals experienced pain from cramps. Additionally, Ng et al. (27) found 72.7% ($N = 32$) of individuals experienced cramps and/or spasms. Rivera et al. (30) reported only 9% of individuals reported experiencing cramps.

Neuropathic pain was reported in three of the included studies. One study used the Douleur Neuropathique–4 [Neuropathic Pain Diagnostic Questionnaire] and reported that 8.6% ($N = 8$) of individuals with ALS experienced neuropathic pain (26). Rivera et al. (30) utilized the Neuropathic Pain Scale. They identified rates of neuropathic pain descriptors, the highest being dull (22%), followed by sharp (18%) and ache (14%). Taga et al. (33) found 62.5% ($N = 10$) of participants

experienced pain with neuropathic-type descriptors such as "electric shock", "burning" "dull", "stabbing", "throbbing", "painful cold", "sharp", "paroxysmal shooting" or "complex regional pain syndrome". An additional study (36), did not find any patients with ALS reporting neuropathic pain.

Discussion

Pain is a prominent symptom with a diverse presentation in ALS. Pooled pain prevalence in the published ALS literature is 60% (95% CI = 50–69%) with a substantial level of between-study heterogeneity. Studies using only validated measures showed a pain prevalence of 65%. Despite between-study heterogeneity was marginally lower for validated pain measures, it was still notably high. There were many different validated pain measures used in the included studies, and there was minimal commonality between the measures and administration methods. This introduces heterogeneity in assessment techniques and subsequently, heterogeneity in the prevalence estimates.

A number of studies ($N = 9$) used tailored measures (e.g., face-to-face or clinical interviews, un-validated questionnaire measures, or retrospective medical record reviews). These measures showed the largest between-study heterogeneity. Due to the lack of standardization for this type of pain detection, the findings may be influenced by factors such as variable reporting, inconsistent classification, and clinically-subjective identification. Tailored measures produced the lowest pooled prevalence of pain estimate (45%). This could indicate a risk of observer or measurement bias, resulting in the under-estimation of pain prevalence.

A recent study also proposed that some individuals do not report pain due to it being regarded as a minor symptom compared to other aspects of the disease (3). This may further contribute to under-reporting of pain, as individuals might not be asked about their pain in a direct or structured way. Conversely, in a small subset of studies, when combining tailored with validated measures, there was still a high level of between-study heterogeneity. This also suggests that this mixed methodology in identifying cases of pain might induce bias and actually over-estimate prevalence of pain, as shown by the 76% pooled prevalence estimate.

Due to under and over estimation of pain, both may have repercussions for timely intervention and selecting pharmacological or nonpharmacological treatments. Standardized or equivalent validated assessment methods of pain are needed in ALS, to lower current levels of heterogeneity. Considering the importance of pain to ALS patients, its potential in limiting participation in activities of daily living and reducing quality of life (e.g., (21,29)); there is a clear need for increased attention from clinicians and researchers. Consensus on which tools should be used to assess, monitor and compare symptoms of pain in an ALS-specific population will increase the likelihood of ameliorating distressing experiences of pain more effectively.

In terms of characteristics of pain, our findings demonstrate that the most commonly reported location of pain for ALS patients is in the upper limbs, but can also occur in other regions, including the lower limbs, head, back and neck. This observation concurs with previous findings (9). Future studies should look to map specific regions(s) of ALS onset and the experience of pain. This may provide further insight in to the impact of the condition. Cramps and spasms were the most commonly reported types or sources of pain in ALS (38). A previous systematic review found that that there was no evidence in favor of particular interventions for the management of muscle cramps (39) but the UK NICE guidelines for assessment and management for ALS provide some recommendations (5). However, they do not discuss these recommendations in the general context of pain.

Neuropathic pain, or pain with neuropathic-type descriptors, was also reported in three of the studies included in this review (26,30,33). It is important to note that two of these studies (26,30) used measures specifically designed to measure neuropathic pain. The other study used qualitative neuropathic-type descriptors (33). Of note, one study (36) indicated that neuropathic pain is not prevalent in ALS. This type of pain is often mechanistically complex and experienced unpredictably by patients (40,41), but has several potential pharmacological management pathways (42). However, as described in a previous review (2) there is limited exploration or understanding of neuropathic pain or prevalence in ALS.

Pain is a personalized experience throughout the trajectory of disease progression for people living with ALS. It has been reported to span from physical to mental pain (3). The qualitative experience of pain may be paramount in understanding how people perceive, process and adapt to the pain in their lives. As such, while standardized detection and quantification of pain are important, there should be flexibility to record specific qualities and experiences of the pain. This will aid in understanding the encompassing nature and impacts of pain, as well as inform palliative care needs at an individual patient level.

Limitations

There are several limitations to this review. Firstly, there were fewer data and less information available for the pain characteristics (such as intensity

and type) and location, primarily due to variable and subjective reporting between and within studies. This resulted in merging of characteristics based on common elements and this reductionism of findings might limit conclusions. Future research should look to characterize pain more specifically in terms of etiology, source, intensity, and type to further elucidate this symptom. Pain was most commonly associated with cramps in the research, which may have skewed the findings. However, there were different sources of pain reported throughout included studies.

Further research is needed to understand the impact of experience of ALS patients longitudinally over the course of the disease, in relation to genetic phenotype, cognitive and behavioral impairment. Further exploration of characteristics and prevalence of pain across the motor neurone disease spectrum (such as progressive muscular atrophy, progressive bulbar palsy, flail limb syndrome, and primary lateral sclerosis) would be of value. Due to the importance of first identifying the prevalence of pain and its characteristics prior to management, this review did not examine pharmacological and nonpharmacological approaches to treatment of pain in ALS. Future research should include the preferences of ALS patients in receiving treatment for pain.

Conclusion

This systematic review and meta-analysis indicate that physical pain is a symptom occurring for two-thirds of all ALS patients' experience. Considering the variability and heterogeneity in reported pain prevalence and outcome measures used in the included studies in this review, there is a clear need for a standardized approach using validated tools that have both clinical and research utility to characterize and assess pain in ALS. Better characterization of pain will support more effective management and treatment of this symptom to promote increased quality of life and wellbeing in ALS patients.

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Declaration of interests

The authors report no conflict of interest.

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