Movement Disorders
CLINICAL PRACTICE

REVIEW

Pain in Multiple System Atrophy a Systematic Review and Meta-Analysis

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Abstract: Background: Individuals with multiple system atrophy (MSA) often complain about pain, nonetheless this remains a poorly investigated non-motor feature of MSA.

Objectives: Here, we aimed at assessing the prevalence, characteristics, and risk factors for pain in individuals with MSA.

Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines, we systematically screened the PubMED, Cochrane, and Web of Science databases for papers published in English until September 30, 2022, combining the following keywords: "pain," "multiple system atrophy," "MSA," "olivopontocerebellar atrophy," "OPCA," "striatonigral degeneration," "SND," "Shy Drager," and "atypical parkinsonism."

Results: The search identified 700 records. Sixteen studies provided information on pain prevalence in cohorts of MSA individuals and were included in a qualitative assessment based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. Thirteen studies (11 cross-sectional, two longitudinal) scored ≥14 points on QUADAS assessment and were included in a quantitative analysis, pooling data from 1236 MSA individuals. The resulting pooled prevalence of pain in MSA was 67% (95% confidence intervals [CI] = 57%–75%), and significantly higher in individuals with MSA of parkinsonian rather than cerebellar type (76% [95% CI = 63%–87%] vs. 45% [95% CI = 33%–57%], $P = 0.001$). Pain assessment tools and collected information were highly heterogeneous across studies. Two studies reported pain treatment strategies and found that only every second person with MSA complaining about pain had received targeted treatment.

Conclusions: We found that pain is a frequent, but still under-recognized and undertreated feature of MSA. Further research is needed to improve pain detection and treatment in MSA.

Multiple system atrophy (MSA) is a rare, orphan neurodegenerative disorder affecting adults, characterized by poor levodopa (L-dopa) responsive parkinsonism, cerebellar ataxia, and autonomic failure in various combinations.[1,2] Based on the predominant motor phenotype, a parkinsonian (MSA-P) and a cerebellar (MSA-C) variant of MSA are distinguished.[2] Besides the core motor and autonomic features, a broad constellation of non-motor symptoms, including pain, may develop during MSA rapidly progressive disease course, leading to increasing disability and an average survival of 6 to 10 years from disease onset.[2]

Despite multiple ongoing research efforts and preliminary evidence of neuroprotection for stem cell- and ubiquinol-based

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strategies, to date there is no cure capable of halting or substantially slowing the progression of MSA.[3–5] MSA physicians and allied healthcare professionals are, therefore, called to promptly respond to the dynamic care needs of individuals with MSA with multidisciplinary, individualized treatment strategies aimed at alleviating both the patients' and, indirectly, the caregivers' burden.[5]

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[6] Pain has been extensively studied in the setting of Parkinson's disease (PD), where it is increasingly recognized to affect ~30% to 80% of affected individuals and significantly impact on their quality of life (QoL).[7] Individuals living with MSA may be even more prone to develop painful conditions compared to people living with PD or other atypical parkinsonian syndromes,[8] but data on the prevalence, characteristics, and risk factors for pain in MSA are fragmentary,[9] leaving such disabling feature often overlooked and undertreated in clinical practice.

Here, we performed a systematic review and meta-analysis to appraise the current understanding of pain in MSA with a focus on its prevalence, associated features, assessment tools, and treatment strategies.

Methods

Paper Selection

We performed a systematic review of the literature in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[10] The PubMed, Cochrane, and Web of Science databases were systematically screened for articles on pain in individuals diagnosed with MSA, by using a combination of the following keywords: "pain," "multiple system atrophy," "MSA," "olivopontocerebellar atrophy," "OPCA," "striatonigral degeneration," "SND," "Shy Drager," and "atypical parkinsonism." The search was limited to articles in English published until September 30, 2022 and excluded case reports or reviews. Only original papers reporting at least information on pain frequency in a cohort of individuals with MSA diagnosed according to established consensus criteria or by expert neurologists were included for quality assessment. The references of selected articles were crosschecked for additional eligible papers.

Quality Assessment and Risk of Bias

Two raters (N.C. and B.C.) independently assessed the quality of the papers by means of the modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS), a quality assessment tool that has been previously used in systematic reviews on pain in PD and other atypical parkinsonian disorders.[11–13] We used a cutoff of ≥14 points to identify papers of acceptable quality to be included in the quantitative synthesis.[13] Score disagreements between the raters were resolved with case-by-case discussions and, whenever necessary, by an independent senior reviewer (A.F.) The inter-rater agreement was calculated by means of Cohen's κ statistics.

Data Extraction and Synthesis

Data extraction was performed independently by two authors (N.C. and B.C.) using a shared data extraction table. The extracted variables included author name, journal, publication year, study design, sample size, applied diagnostic criteria, gender, mean age, disease duration of the individuals at the time of study recruitment, MSA-C/-P subtype, percentage of patients reporting pain, and pain assessment tools. In case of missing data, we contacted the corresponding authors of the respective papers asking for the missing information. Up to two reminders were sent to non-responders. Whenever available, additional information on other pain descriptors (eg, type of pain, intensity, and location) and pain management was collected.

Pooled Prevalence of Pain Across Identified MSA Cohorts

Based on the information reported in the papers retained for quantitative synthesis, we calculated the pooled prevalence of pain in individuals with MSA and summarized the data by means of a forest plot. We additionally performed subgroup analyses to compare pain prevalence between individuals with MSA-P versus MSA-C and between female versus male MSA individuals. Random-effect analysis underwent χ^2 test for heterogeneity quantified by the I^2 statistics. Statistical analysis was performed with IBM SPSS Statistics version 29.0 and Stata version 15.1 (StataCorp, College Station, TX). Two-sided $P < 0.05$ was considered statistically significant.

Data Sharing

No original data has been generated for this review. The first and the last author confirm that the data supporting the present findings are available in the article and it's Supporting Information. The review was registered in the PROSPERO database (registration number: CRD42022359933).

Results

Systematic Review and Quality Assessment

Our search identified 700 records. After removing duplicates and papers not written in English, 487 titles and abstracts were screened. Forty-one papers were selected for full-text screening. Among them, 14 fulfilled the criteria for inclusion in the quality assessment. Two additional relevant papers were retrieved by cross-checking the references of selected papers. Sixteen papers (one retrospective, 13 cross-sectional, and two longitudinal

studies) were included in the quality assessment. The modified QUADAS scores of these papers are provided in the Table S1. Inter-rater agreement in the quality assessment was optimal (Cohen's $\kappa = 0.82$; $P < 0.001$). Three papers did not fulfill the predefined QUADAS quality cutoff ≥14 for inclusion in the final quantitative analysis. These included two papers exploring the so called "coat-hanger pain" and other symptoms associated with orthostatic hypotension,[14,15] and one retrospective study exploring pain prevalence in individuals with MSA, yet with a high degree of methodological heterogeneity.[16] The results of the paper selection process are summarized in Fig. 1.

The papers retained for the final quantitative synthesis (n = 13) included 11 cross-sectional and two longitudinal studies, pooling data from 1236 individuals with MSA. Among them, 57% (n = 639) were males and 43% (n = 482) were females. Six papers provided information on the MSA phenotype (cumulative n = 748), with 51% (n = 379) of the individuals presenting predominantly with MSA-P and 49% (n = 369) with MSA-C. MSA was diagnosed according to the 2008 consensus criteria[17] in 10 papers,[8,18–26] whereas three papers did not provide information on the applied diagnostic criteria.[27–29] Assessing the prevalence of pain in a cohort of individuals with MSA was the primary objective in six of the 13 studies included in the quantitative synthesis,[8,19,20,22–24] whereas in the remaining studies (n = 7)[18,21,25–29] the prevalence of pain was reported as a secondary outcome. The key information about the analyzed studies is summarized in Table 1.

Prevalence of Pain in MSA

Pooling the results of all studies included in the quantitative analysis, 761 of the 1236 individuals with MSA complained about pain, with a prevalence range of 40% to 88% and an estimated pooled prevalence of 67% (95% CI = 57%–75%) (Fig. 2). The I^2 statistics highlighted a high heterogeneity in the reported prevalence of pain across studies ($I^2 = 88.78\%$, $P < 0.01$). Studies assessing pain among the secondary outcome measures reported a higher, although not statistically significant prevalence of pain compared to studies exploring pain prevalence as primary outcome measure (73% [95% CI = 61%–83%] vs. 59% [95% CI = 45%–72%], $P = 0.114$) (Fig. 2).

Four studies reported a higher prevalence of pain in individuals with MSA-P compared to MSA-C,[18,23,24,26] whereas two others did not detect any statistically significant difference between the MSA-P and MSA-C subtypes.[19,25] Across studies, the pooled prevalence of pain was significantly higher in individuals with MSA-P than MSA-C (76% [95% CI = 63%–87%] vs. 45% [95% CI = 33%–57%], $P = 0.001$). The prevalence of pain was, however, highly heterogeneous both for the MSA-P ($I^2 = 82.89\%$, $P < 0.01$) and MSA-C ($I^2 = 69.77\%$, $P = 0.01$) subtypes (Fig. 3A).

None of the papers included in the final analysis specifically addressed sex- or gender-related differences in the pain prevalence in MSA. One study provided the frequency of male and female MSA individuals with any kind of pain separately.[19] The corresponding authors of all included studies were contacted to retrieve data on the prevalence of pain in male and female individuals with MSA separately. Three authors kindly provided this additional information.[18,21,24] Pooling data of n = 480 individuals with MSA (210 females, 270 males), we found no difference in the prevalence of pain between male (52% [95% CI = 42%–61%]) and female (66% [95% CI = 49%–81%]) individuals with MSA ($P = 0.143$) (Fig. 3B).

Pain Features and Risk Factors for Pain in MSA

Three studies reported information on the localization of pain. Legs, arms, neck, and trunk were the most frequently affected body regions, and pain often affected more than one body region.[19,20,24] Musculoskeletal pain was the most frequently reported pain type in MSA individuals according to three studies, which also described neuropathic pain forms, mostly radicular and dystonic.[20,22,24] One additional study reported mixed pain (i.e., with both nociceptive and neuropathic components) to be most frequent in MSA individuals (46%), followed by neuropathic (36%) and nociceptive pain (18%, Table 2).[21]

The association between pain frequency and/or intensity and disease duration or disease stage was addressed in one study only, which found no correlation.[24] Overall, pain has been reported both in the early[20] and advanced stages[27] of MSA and to precede the onset of core MSA motor or autonomic features in some cases.[16,20]

Two studies found a significant positive association between depression, anxiety, and pain intensity, as well as lower subjective pain thresholds in MSA individuals.[21,24]

Pain Assessment Tools

Different pain assessment tools were used across studies, with many studies using more than one tool (Table 1).

Three studies each used the visual analog scale[19–21] or the short form of the McGill pain questionnaire (SF-McGill),[21,22,24] to quantify pain intensity and the German Pain Questionnaire (Deutscher Schmerz Fragebogen) was used in one study.[19]

Neuropathic pain components were investigated with the Neuropathic Pain Symptom Inventory[21] and the Leeds Assessment of Neuropathic Symptoms and Signs[24] in one study each.

General health status and quality of life questionnaires were also applied, including the pain item of the European Quality of Life 5 Dimensions questionnaire (EQ-5D, used in six studies),[18,25–29] the "bodily discomfort" item of the Parkinson's Disease Questionnaire–8 items (PDQ8),[27] and the 36-Item Short Form Survey (SF-36).[26]

Other studies used the item 27 of the Parkinson's Disease Non-Motor Symptom Scale (NMSS),[23] the item 1.9 of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[24] or the pain item of the Palliative Care Outcomes Scale (PCOS).[27]

One study used a semi-structured interview for a multidimensional pain assessment.[8]

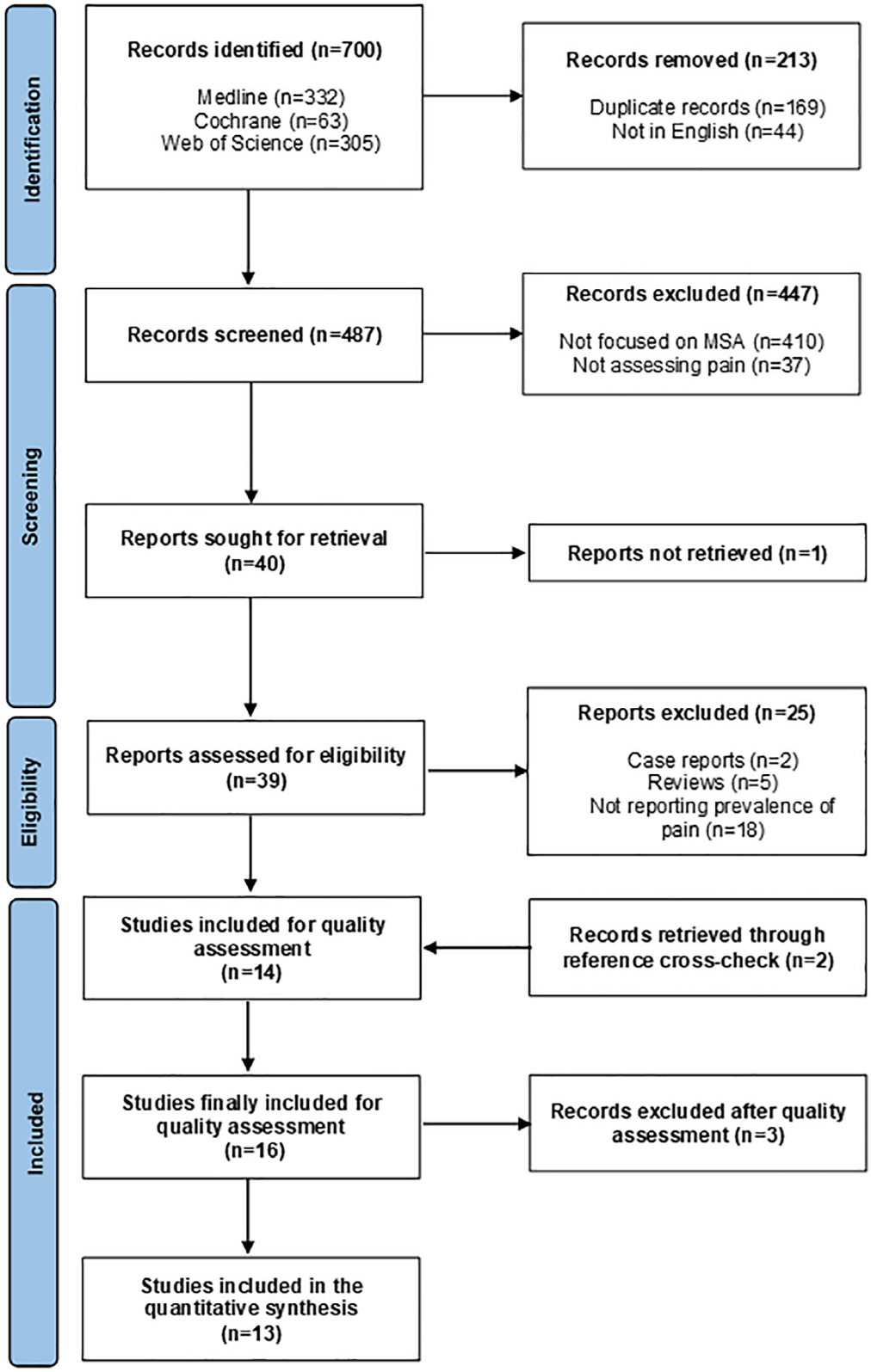

FIG. 1. Preferred reporting item for systematic reviews and meta-analysis (PRISMA) flow diagram summarizing the paper selection process.

TABLE 1 *Characteristics of the papers on pain in MSA included for quality assessment and quantitative synthesis in the present systematic review.*

Reference	Country	Pain prevalence primary outcome?	Study design	Diagnostic criteria	Sample size (n)	Gender (males, %)	MSA phenotype (MSA-P, %)	Mean age (years)	Mean disease duration (years)	Pain assessment tools	Pain prevalence (%)
Xiao et al[18]	China	No	Cross-sectional	Gilman 2008 (probable)	380	56	46	60.34 ± 9.28	2.63 ± 1.48	EQ-5D-5L	54
Sung et al[20]	Korea	Yes	Cross-sectional	Gilman 2008	33	52	n.a.	61.1 ± 8.3	2.1 ± 1.5	VAS	61
You et al[19]	China	Yes	Cross-sectional	Gilman 2008	65	66	n.a.	62.65 ± 8.13	2.35 ± 2.10	VAS, DSF	46
Ory-Magne et al[21]	France	No	Cross-sectional	Gilman 2008	14	43	100	64.4 ± 7.3	4.3 ± 1.7	VAS, SF-McGill, NPSI	79
Yust-Katz et al[22]	Israel	Yes	Cross-sectional	Gilman 2008	36	58	n.a.	71 ± 9.7	5 ± 3.4	SF-McGill	64
Zhang et al[23]	China	Yes	Cross-sectional	Gilman 2008 (probable)	172	58	44	60.03 ± 7.03	2.72 ± 1.60	NMSS item 27	40
Kass-Iliyya et al[24]	UK	Yes	Cross-sectional	Gilman 2008 (probable)	21	43	67	63.6 ± 1.6	3.2 ± 1.5	MDS-UPDRS item 1.9, SF-McGill, LANSS	81
Calvert et al[28]	UK	No	Cross-sectional	n.a.	17	65	n.a.	66.9 ± 9.2	n.a.	EQ-5D-3L	71
Higginson et al[27]	UK	No	Longitudinal	n.a.	17	65	n.a.	67 ± 8	5.9 ± 4	EQ-5D-3L, PDQ8, POS	88
Winter et al[25]	Germany	No	Cross-sectional	Gilman 2008	46	50	61	n.a.	n.a.	EQ-5D-3L	80
Schrag et al[26]	UK, USA, Canada	No	Cross-sectional	n.a.	286	58	n.a.	65.4 ± 9.8	6.3 ± 3.9	EQ-5D-3L	78
Colosimo et al[8]	Italy	Yes	Longitudinal	Gilman 2008	34	62	n.a.	63.5 ± 8.7	3.5 ± 1.8	Semi-structured interview	71
Schrag et al[26]	Europe	No	Cross-sectional	Gilman 2008	115	n.a.	63	n.a.	4.3 [2.9–6.2]	EQ-5D-3L, SF-36	66
Mathias et al[15]	UK	No	Cross-sectional	n.a.	40	n.a.	n.a.	n.a.	n.a.	Semi-structured interview	53[a]
Bleasdale-Barr et al[14]	UK	No	Cross-sectional	n.a.	35	66	n.a.	n.a.	n.a.	Semi-structured interview	51[a]
Tison et al[16]	UK	Yes	Retrospective	Quinn 1994 (probable)	100	67	82	n.a.	n.a.	Retrospective chart review	47

Note: Papers marked in gray were included in the qualitative synthesis, but excluded from the quantitative analysis because they did not reach the ≥14 points QUADAS score cutoff. Age and disease duration are reported as mean ± standard deviation, except for Schrag et al[26] where data is reported as median (interquartile range).

Abbreviations: MSA, multiple system atrophy; MSA-P, multiple system atrophy parkinsonian subtype; EQ-5D-5L, EuroQoL questionnaire 5 dimensions–5 levels; n.a., not available; VAS, visual analog scale; DSF, Deutscher Schmerz Fragebogen (German pain questionnaire); SF-McGill, short-form McGill Pain Questionnaire; NPSI, Neuropathic Pain Symptom Inventory; NMSS, non-motor symptom scale; UK, United Kingdom; MDS-UPDRS, Movement Disorders Society–Unified Parkinson's Disease Rating Scale; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; EQ-5D-3L, EuroQoL questionnaire 5 dimensions-3 levels; PDQ8, Parkinson's disease questionnaire–8 items; POS, palliative outcomes scale; SF-36, short form questionnaire; USA, United States of America.

[a]Reported prevalence refers to "coat-hanger pain".

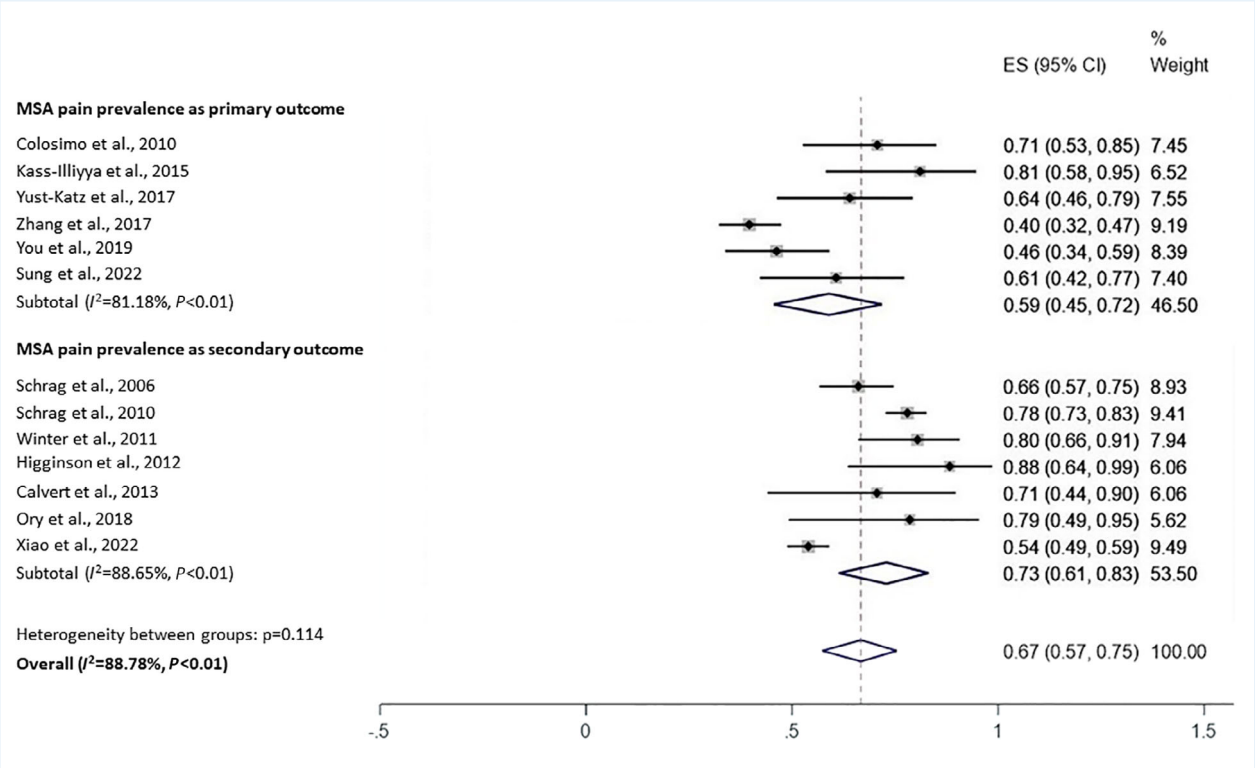

FIG. 2. Forest plot for the analysis of pooled prevalence of pain in individuals with MSA. Studies addressing pain as a primary or secondary outcome are plotted separately. CI, confidence interval; ES, effect size; MSA, multiple system atrophy.

Pain Treatment

Two papers reported information on pain management in individuals with MSA.[19,24] They found that approximately every second individual with MSA (43%–65%) complaining about pain had received any kind of targeted treatment.[19,24] In one study, up to 65% of MSA individuals with pain were on regular analgesic therapy and 24% received treatment for neuropathic pain.[24] In 20%–70% of individuals with MSA reporting painful sensations, an improvement was obtained with the intake of the dopaminergic medication.[19,24] Non-pharmacological pain-relieving interventions included physiotherapy, regular exercise, and other neurorehabilitation measures.[19]

Discussion

This is the first systematic review and meta-analysis specifically addressing pain prevalence and associated features in individuals with MSA. Here, we found that approximately two thirds of individuals with MSA suffer from any kind of pain throughout the disease course. There was considerable heterogeneity in the frequency of pain across the included studies. Such heterogeneity may be due to methodological differences, but could also reflect differences in the disease characteristics of the MSA cohorts studied, including disease duration and other clinical-demographic or social features.

The prevalence of pain in individuals with MSA seems higher compared to other forms of atypical parkinsonism, including corticobasal degeneration and progressive supranuclear palsy (PSP), for which another recent meta-analysis estimated a pooled pain prevalence of 25% and 52%, respectively.[13] Several factors may account for the higher prevalence of pain in MSA individuals: the different distribution of neuropathological changes,[22] a more pronounced spinal cord,[30] or small fiber involvement in MSA individuals that may contribute to an altered pain perception,[31] or ultimately the presence of multiple potentially painful motor and autonomic features typical of advanced MSA stages. On the other hand, the cognitive impairment developing in individuals with PSP might prevent them from recognizing or communicating painful sensations, introducing an additional barrier to pain recognition in clinical practice.

The subgroup analysis confirmed a higher prevalence of pain in individuals with MSA-P compared to MSA-C.[16] Both differences in the clinical presentation (eg, a higher prevalence of rigidity and dystonia) and in the neuropathological substrate (eg, a more prominent degeneration of the basal ganglia that are involved in pain modulation)[7,32] may account for the higher prevalence of pain in the MSA-P compared to the MSA-C phenotype.

In the general population, chronic pain develops more frequently in women than in men.[33] Although one of the identified studies indicated that female individuals with MSA may be more prone to complain about pain,[16] our meta-analysis did not

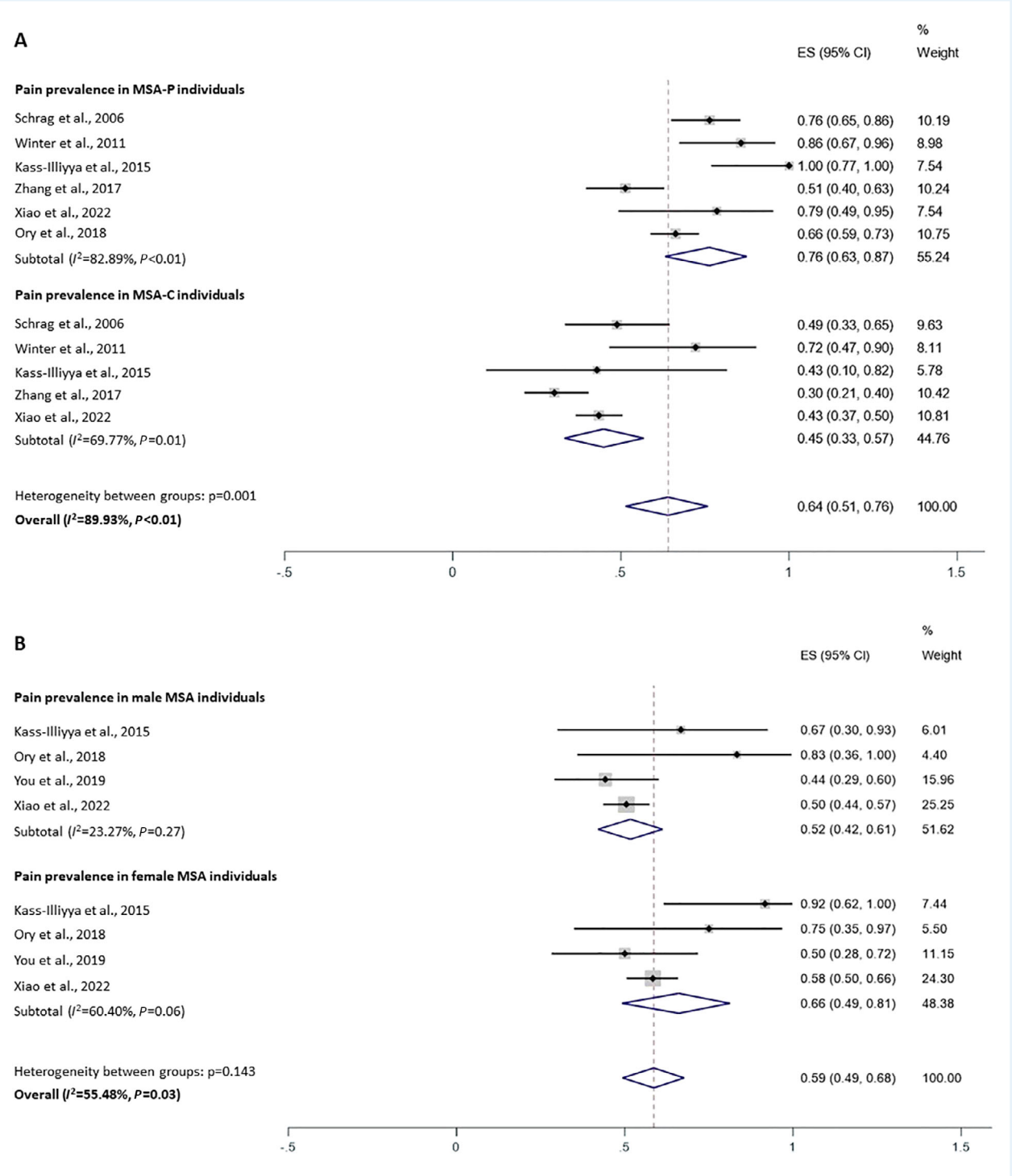

FIG. 3. **(A)** Forest plot for the analysis of pooled prevalence of pain in individuals with MSA-P versus MSA-C; **(B)** Forest plot for the analysis of pooled prevalence of pain in male and female individuals with MSA. CI, confidence interval; ES, effect size; MSA, multiple system atrophy.

identify any difference in pain prevalence between male and female MSA individuals. Such analysis pooled data from four studies only, highlighting the need for further studies on the effects of sex and gender on pain development, perception, and communication in individuals with MSA.[34]

To date, there are no disease-specific validated questionnaires to screen for pain in individuals with MSA, and different generic tools have been used in the analyzed studies (summarized in Table S2). For PD, both a physician-administered pain rating scale, the King's PD pain scale,[35] and a patient-reported pain

TABLE 2 *Most frequent pain localization and types in individuals with MSA as reported by the papers included for quality assessment and quantitative synthesis in the present systematic review.*

Reference	Pain localization	Pain types
Sung et al[20]	Trunk, legs > arms > neck	Musculoskeletal > radicular/neuropathic > central/neuropathic
You et al[19]	Back > neck/shoulders > legs > more than one site > arms	n.a.
Ory-Magne et al[21]	n.a.	Mixed (46%), central neuropathic (36%), nociceptive (18%)
Yust-Katz et al[22]	n.a.	Musculoskeletal (55%) > central (28%) > radicular (9%) > arteritic (1%), neuropathic (5%)
Kass-Iliyya et al[24]	Legs > arms > neck > back	Musculoskeletal > central neuropathic > dystonic > akathisic > radicular[a]
Mathias et al[15b]	Neck > lower back > chest	n.a.
Bleasdale-Barr et al[14b]	Neck > calf > buttock	n.a.
Tison et al[16]	n.a.	Rheumatic (64%), sensory (28%), dystonic (21%), mixed (19%).

Note: Papers marked in gray were included in the qualitative synthesis, but excluded from the quantitative analysis because not reaching the ≥14 points QUADAS score cutoff.
Abbreviations: MSA, multiple system atrophy; n.a., not available; QUADAS, Quality Assessment of Diagnostic Accuracy Studies.
[a]Data not presented in the paper, kindly provided by the authors on request.
[b]Data referring to pain related to orthostatic hypotension.

questionnaire, the King's PD pain questionnaire,[36] have been validated. The development of such tools raised the awareness for painful conditions among healthcare professionals, provided validated outcome measures for pain-targeted clinical trials and may serve as basis for developing MSA-specific pain assessment tools.

Pain is traditionally classified into nociceptive, that is, "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors," and neuropathic, that is, "pain caused by a lesion or disease of the central or peripheral somatosensory nervous system".[37] In the absence of a MSA-specific pain taxonomy, pain classification frameworks used in PD have been sometimes applied to investigate pain in MSA.[20,22,24] These include the differentiation into musculoskeletal, dystonic, radicular/neuritic, akathisic, and joint pain proposed by Goetz et al[38] and revised by Ford et al,[39] the Wasner and Deuschl pain classification framework that distinguishes between PD-related and PD-unrelated pain types,[7] and the most recent one, based on the King's PD Pain Scale,[35] which identifies seven major pain domains: musculoskeletal, chronic, fluctuation-related, nocturnal, orofacial, discoloration, and edema/swelling, radicular.

The studies analyzed here reported nociceptive, neuropathic, and mixed types of pain in MSA individuals.[21] Several of the major PD pain types were also found in MSA individuals, most frequently musculoskeletal pain, followed by radicular and neuritic pain.[20,22,24] However, several of the analyzed studies focused on MSA-related pain only, excluding a priori individuals with painful comorbidities (eg, arthrosis).[19–21,24] Such exclusion criterion likely introduced a selection bias, because nociceptive pain may develop or worsen as a consequence of MSA motor impairment itself. For example, in individuals with marked akinesia, mixed forms of pain are likely to develop, with both a neuropathic component because of the severe central nervous system dysfunction and a nociceptive one because of musculoskeletal pain or pressure sores determined by prolonged immobility. PD pain classification frameworks may also bring about some caveats when applied to MSA settings. Whereas in fact some PD-specific pain types develop less frequently in MSA (eg, fluctuation-related pain), others may occur earlier and in a more severe form in MSA individuals. Examples are the so-called coat-hanger pain (ie, painful sensation in the neck and shoulder region on standing because of orthostatic hypotension),[14,15] painful dystonic postures sometimes exacerbated by L-dopa intake[2,16,24] or "bowel pain," reflecting gastrointestinal or urogenital dysfunction.[40] These types of pain are only partially investigated by the currently available pain assessment tools, which, therefore, carry a potential detection bias when applied to individuals with MSA.

The mechanisms underlying neuropathic forms of pain in MSA are not fully understood to date. Reduced subjective and objective pain thresholds have been reported in MSA individuals[21,41–43] and both peripheral, that is, large and small fiber neuropathy,[31,44–47] as well as central mechanisms likely contribute to such phenomenon. Within the central nervous system, nociception may be facilitated by neurodegenerative changes affecting the spinal cord,[41,42,48,49] or supraspinal pain-processing relays, including serotoninergic and noradrenergic brainstem nuclei, thalamus, and basal ganglia.[9,21,50] This is in line with the higher prevalence of pain observed in MSA-P compared to MSA-C individuals.[13] Besides the disruption of dopaminergic and noradrenergic networks, impaired serotoninergic transmission may also contribute to pain development in MSA. A bidirectional relationship between pain and depression is well

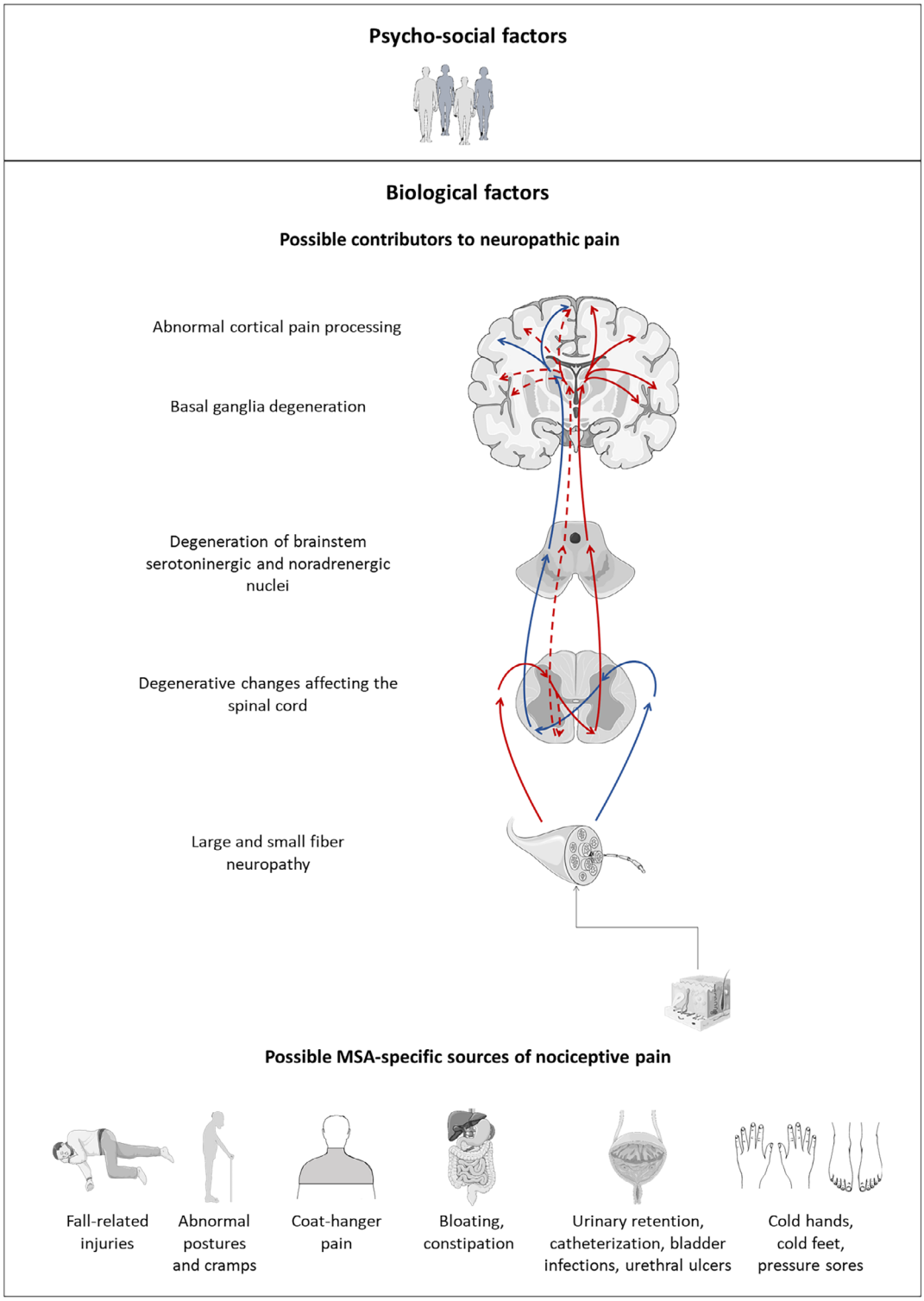

FIG. 4. Putative factors contributing to pain development in individuals with multiple system atrophy. Red line: medial pain pathway; blue line: lateral pain pathway. The figure was generated with Microsoft Power Point using images from Servier Medical Art (https://smart.servier.com/), provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license (https://creativecommons.org/licenses/by/3.0/).

recognized in the general population.[33] This has been also found in clinical[21,24] and in neuroimaging studies, which showed lower serotoninergic radiotracer uptake in the raphe nuclei of MSA individuals with fatigue, apathy, and pain.[51] Ultimately, a complex, multidimensional, and dynamic interplay between biological, social, and psychological factors likely contributes to determine, maintain, and exacerbate pain perception in individuals with chronic painful conditions, including MSA[33] (Fig. 4).

The Declaration of Montreal states that "access to pain management is a fundamental human right."[52] Nonetheless, here, we found that only every second person with MSA complaining about pain received targeted treatment. Pain pharmacological interventions including NSAIDs, opiates, and cannabinoids[53] were reported in MSA case-reports and case-series, but no randomized clinical trials for treating pain in MSA individuals are available to date.[19,24] In PD, dopaminergic medications may help to relieve pain,[7,54,55] especially when fluctuation-related. In MSA, motor and non-motor fluctuations are rare, do not respond well to dopaminergic treatment, and dystonia, especially when affecting the craniocervical region, may worsen under L-dopa intake.[56] Under this point of view, the insufficient response of pain to dopaminergic medications in individuals with MSA might be interpreted as a non-motor form of poor L-dopa responsiveness, mirroring what is observed for parkinsonian motor symptoms at established stages of the disease. Nonetheless, pain relief following L-dopa administration has been anecdotally reported in MSA individuals.[19,24] An optimized management of some distressing MSA features, including botulinum toxin for focal dystonia[57] or targeted strategies for cardiovascular,[58] bladder, and bowel autonomic disturbances may ultimately represent additional MSA-specific pain therapeutic strategies. Among non-pharmacological measures, regular exercise, physiotherapy, and scrambler therapy have been also reported to contribute to pain reduction in MSA,[19,59] possibly preventing painful contractions and pressure sores.

Despite adhering to the PRISMA rules for systematic reviews, the retrieved evidence determined some limitations of the present study. First, inclusion and exclusion criteria varied significantly across the analyzed studies. Second, the study designs were also highly heterogeneous, with approximately half of the papers assessing pain as a secondary outcome. Third, the pain assessment tools differed across studies, likely influencing the pain detection accuracy. All these factors may have indirectly impacted on the accuracy of the pooled data analysis and ultimately prevented a systematic assessment of the most frequent pain types and localizations in MSA.

Nonetheless, this review pointed out multiple research needs, which future studies should focus on or consider in their methodological design. These unmet needs fall into three main areas:

(1) Characterization of pain epidemiology in MSA, which should focus on: stratifying pain prevalence according to the MSA phenotype and disease phase, with a spotlight on both the prodromal and advanced disease stages; distinguishing between nociceptive and neuropathic pain types, while taking into account the background prevalence of common painful conditions in the aging population; understanding the role of sex, gender, comorbidities, other MSA-related and unrelated biological, psychological, and social factors contributing to pain development and maintenance in MSA individuals.

(2) Implementation of MSA-specific pain screening tools, adapting currently available pain classification frameworks, clinical scales, and patient questionnaires to the peculiar setting of MSA.

(3) Development of MSA-specific pain treatment strategies, with randomized-controlled trials to prove the efficacy of different pharmacological and non-pharmacological therapeutic approaches.

Conclusion

Pain is a common, distressful, yet underdiagnosed and an undertreated non-motor feature in MSA. In the absence of disease-modifying therapies, improving pain recognition and management is highly warranted to improve the QoL of individuals with MSA and their caregivers throughout the disease course.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

N.C.: 1B, 1C, 2B, 3A
B.C.: 1C, 3B
F.L.: 1C, 3B
L.K.: 1C, 3B
G.G.: 1B, 1C, 2A, 2B, 3B
J.W.: 1A, 3B
A.S.: 1A, 3B
L.Z.: 1A, 3B
K.B.: 3B
R.C.: 1A, 3B
A.S.: 1A, 3B
R.G.: 1A, 3B
S.K.: 1A, 3B
W.P.: 1A, 3B
K.S.: 1A, 3B
G.W.: 1A, 1B, 3B
A.F.: 1A, 1B, 1C, 2B, 2C, 3B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board and the informed patient consent was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. (Modified) QUADAS scores for eligible studies for the quality assessment.

The global score has been calculated as a rounded up mean of the two independent scores. Papers highlighted in gray did not reach the criteria (global score ≥14) for inclusion in the quantitative synthesis.

Table S2. Pain assessment tools potentially useful to explore pain in MSA.