RESEARCH ARTICLE

Pain in Multiple System Atrophy: A Community-Based Survey

Nicole Campese, MD,[1] Georg Göbel, MSc, PhD,[2] Julia Wanschitz, MD,[1] Andreas Schlager, MD, MSc,[3] Bianca Caliò, MD,[1] Fabian Leys, MD, PhD,[1] Pam Bower,[4] Larry Kellerman,[4] Laura Zamarian, PhD,[1] Kirsty Bannister, PhD,[5] Kallol Ray Chaudhuri, MD, DSc,[5,6] Anette Schrag, MD, FRCP,[7] Roy Freeman, MD,[8] Horacio Kaufmann, MD,[9] Roberta Granata, MD,[1] Stefan Kiechl, MD,[1] Werner Poewe, MD,[1] Klaus Seppi, MD,[1] Gregor Wenning, MD, PhD, MSc,[1†] and Alessandra Fanciulli, MD, PhD[1*]

[1]*Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria*
[2]*Institute for Medical Statistics and Informatics, Medical University of Innsbruck, Innsbruck, Austria*
[3]*Department of Anesthesiology and Intensive Care Medicine, Medical University of Innsbruck, Innsbruck, Austria*
[4]*Mission MSA (formerly The Multiple System Atrophy Coalition) Inc, McLean, Virginia, USA*
[5]*Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom*
[6]*Parkinson Foundation International Centre of Excellence, Kings College Hospital, London, United Kingdom*
[7]*Department of Clinical and Movement Neurosciences, University College London, London, United Kingdom*
[8]*Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA*
[9]*Department of Neurology, Dysautonomia Center, New York University Grossman School of Medicine, New York, New York, USA*

ABSTRACT: Background: Pain is a frequent yet poorly characterized symptom of multiple system atrophy (MSA). Understanding the factors influencing pain and its burden is crucial for improving the symptomatic treatment and quality of life of MSA individuals.
Objective: This study aimed at assessing the prevalence, characteristics, and current treatment strategies for pain in MSA.
Methods: A community-based, online survey was conducted from February to May 2023. Invitations were extended to MSA individuals and informal MSA caregivers through patient advocacies and social media.
Results: We included 190 persons with MSA and 114 caregivers. Eighty-seven percent of MSA individuals reported pain, which was more prevalent among women (odds ratio [OR]: 6.38 [95% confidence interval, CI: 1.27–32.08], $P = 0.025$) and low-income groups (OR: 5.02 [95% CI: 1.32–19.08], $P = 0.018$). Neck and shoulders (58%), back (45%), and legs (45%) were mostly affected. In the neck and shoulders, pain was associated with MSA core features, like orthostatic intolerance (OR: 4.80 [95% CI: 1.92–12.02], $P = 0.001$) and antecollis (OR: 3.24 [95% CI: 1.54–6.82], $P = 0.002$). Seventy-six percent of individuals experiencing pain received treatment, mostly nonsteroidal anti-inflammatory drugs (47%), acetaminophen (39%), and opioids (28%). Only 53% of respondents reported at least partial satisfaction with their current pain management. Pain mostly impacted work, household activities, and hobbies of MSA individuals, and caregivers' social activities.
Conclusions: Pain is more prevalent than previously reported in MSA and particularly affects women and low-income groups. Despite its frequency, pain management remains suboptimal, highlighting an urgent therapeutic need, likely entailing an optimized management of MSA core motor and non-motor features. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: multiple system atrophy; pain; non-motor symptoms; quality of life

*__Correspondence to:__ Ass. Prof. Dr. Alessandra Fanciulli, Department of Neurology, Medical University of Innsbruck, Anichstraße 35, A-6020 Innsbruck, Austria; E-mail: alessandra.fanciulli@i-med.ac.at

†Author deceased during manuscript preparation.

Relevant conflicts of interest/financial disclosures: The authors have no conflict of interest to disclose related to the content of this article.

Received: 13 May 2024; **Revised:** 12 July 2024; **Accepted:** 17 July 2024

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29961

Twenty percent of adults in the United States suffer from chronic pain, a distressful condition defined as an unpleasant sensory and emotional experience associated with, or resembling that due to, actual or potential tissue damage.[1,2] Pain is even more frequent in individuals with chronic neurological conditions like Parkinson's disease (PD)[3,4] and substantially impacts on disability, quality of life, and health-care costs.[4]

Multiple system atrophy (MSA) is a rare, rapidly progressive neurodegenerative disorder, characterized by a combination of autonomic failure, poorly levodopa responsive parkinsonism, cerebellar ataxia, and pyramidal signs.[5,6] There is currently no treatment capable of halting MSA disease course, and medical care aims at alleviating symptoms with multidisciplinary approaches.[7]

A recent meta-analysis found that two-thirds of MSA individuals may suffer from pain.[8] Most of the available studies, however, focused on individuals referred to specialized MSA centers,[8] whereas more advanced patients or those living in underserved areas, who are potentially at higher risk of developing painful complications, remained understudied so far. Knowledge of MSA-related pain characteristics, risk factors, management strategies, and overall burden on daily activities of affected individuals and their caregivers is also limited.

To answer these gaps in knowledge, we performed a community-based survey on pain in individuals with MSA and on pain-related burden of MSA caregivers.

Patients and Methods

Study Design, Study Population, and Recruitment Strategy

To facilitate the participation of people with reduced mobility or living in remote areas, a web-based, cross-sectional study design was adopted. Individuals with MSA and informal MSA caregivers were invited worldwide via US- and Europe-based advocacies and social media posts (Facebook, X, LinkedIn, and Instagram) to complete dedicated online questionnaires between February 13 and May 6, 2023. To minimize potential recruitment biases, both MSA individuals with and without pain were explicitly invited to take the survey.

Ethical Approval and Informed Consent

This study was approved by the Innsbruck Ethical Committee, followed the Declaration of Helsinki and the European Data Protection Regulation. All participants provided their electronic informed consent prior to accessing the surveys.

Questionnaire Development

In a purposing phase of the project, we performed a systematic review of the literature on pain in MSA[8] and appraised pain-related contents on social media, MSA patients' forums, and self-support groups. Then, the first and the last authors developed the first draft of two questionnaires, one for MSA individuals and one for informal MSA caregivers, which were critically reviewed multiple times by a task force of movement disorders, pain experts (the authors of this publication), 2 MSA patients (1 with multiple system atrophy-parkinsonian variant [MSA-P] and 1 with multiple system atrophy-cerebellar variant [MSA-C]), and two informal MSA caregivers. The final version of the questionnaires is provided in (Data S1 and Data S2). Both caregivers of alive MSA individuals and caregivers of deceased persons with MSA were invited to participate in the study.

The questionnaires covered the following domains:

- *Patient questionnaire*: socioeconomic and clinical information, pain presence and characteristics (including a pain intensity Visual Analog Scale [VAS]), management, impact on activities of daily living, and health status evaluated using the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L).[9]
- *Caregiver questionnaire*: caregivers' socioeconomic and clinical information and health status (evaluated using the EQ-5D-5L); patients' socioeconomic and clinical information, pain presence, characteristics, management, and impact on caregiver's burden and activities of daily living. In the case of former caregivers of deceased persons with MSA, questions referred to the last year of life of the person cared for.

The questionnaires were developed in both English and German lay language, were reviewed by a certified translator for consistency, and by the patient and caregiver representatives for meaningfulness and readability. The questionnaires were then implemented on a user-friendly web-based platform accessible from laptops and mobile phones (REDCap[10,11]) hosted at the Innsbruck Medical University.

Data Cleaning

After survey closure, the collected questionnaires were checked for completeness of a minimal dataset and plausibility.

The minimal dataset consisted of the following entries:

- *Patient questionnaire*: age, gender, diagnosis, and information on the presence or absence of pain in the previous 30 days.

- *Caregiver questionnaire*: caregiver's age, gender, and relationship to the patient; patient's age, gender, diagnosis, and information on the presence or absence of pain in the previous 30 days.

Following the 2022 MDS MSA diagnostic criteria[6] and published MSA natural history studies,[12,13] a diagnosis of MSA was considered implausible in the case of the following:

- Disease onset ≤30 years of age
- Absence of both clumsiness/slowness of movements (bradykinesia), problems with coordination (ataxia) and autonomic dysfunction (ie, either dizziness, lightheadedness, or blackouts in the upright position or bladder problems [see Data S1, S5 and Data S2, S6])
- Disease duration ≥20 years (given that neuropathologically proven MSA cases with 15 years of disease duration were anecdotally described).[14]

Questionnaires with incomplete or implausible minimal datasets were excluded from further analysis.

Statistical Analysis

Qualitative variables were summarized by frequency (percentage), whereas quantitative variables were summarized by median (25th; 75th percentile). In the case of missing data, the available sample size is presented in brackets. Qualitative variables were analyzed using the Pearson's χ^2 or Fisher–Freeman–Halton test (if $n < 5$). Quantitative variables were analyzed using the T-test or Mann-Whitney *U* test. Binary logistic regression analysis was used to develop multivariable regression models, and the Hosmer–Lemeshow test was used to compare the observed and expected event rates of logistic regressions models. The presence of pain was defined as a self-reported perception of any kind of pain, irrespective of its intensity, frequency, or persistence in the 30 days before survey completion. First, we compared the clinical-demographic characteristics of MSA individuals with and without pain in a univariate fashion. Based on the available literature and clinical plausibility, variables potentially relevant for pain development and showing *P*-values ≤0.2 at univariate comparison were selected for multivariable binary logistic regression analysis. In the case of significant bivariate correlations between variables, binary regression models were also tested for interactions. The same approach was adopted to analyze clinical-demographic features associated with painful sensations in different body regions. Information on pain management and impact on activities of daily living of MSA individuals was summarized in a descriptive fashion.

The demographic characteristics and medical history of caregivers of MSA individuals with and without pain were compared using a univariate approach, and the impact of the pain of the person with MSA being cared for on the caregiver's daily life was tabulated per domains. The caregiver questionnaires were further used to explore pain characteristics in very advanced MSA stages, by comparing the information provided by caregivers of alive MSA individuals and caregivers of deceased persons with MSA, the latter concerning the last year of life of the person cared for.

Due to the explorative nature of the study, no correction for multiple testing was applied, and no statistical imputation was operated for missing values. IBM SPSS Statistics, version 29.0, was used for statistical analysis. Two-tailed *P*-values <0.05 were considered statistically significant, except when selecting variables for the multivariate models, for which *P*-values ≤0.2 were considered.

Data Sharing

The first and last authors take responsibility for the integrity of the data. Data supporting the findings of this study that are not reported here are available upon reasonable request from any qualified investigator.

Results

Patient Responses

Study Population

Two-hundred and sixty-four MSA individuals signed the electronic informed consent, and 190 questionnaires were retained for final analysis after data cleaning (Fig. S1).

The median age of MSA survey participants was 62 [55; 69] years, disease duration was 5 [4; 7] years, and 54% of them were female. Respondents most frequently lived in North America (66%), followed by Europe (28%), Oceania (3%), and Asia (2%). Ninety-one percent of the respondents were of White ethnicity. Thirty-four (n = 65/190) percent reported a diagnosis of MSA-P, 52% (n = 98/190) MSA-C, and 14% (n = 27/190) did not specify the clinical phenotype.

Prevalence of Pain and Associated Features

Eighty-seven percent of MSA individuals reported painful sensations.

Univariate analyses (Table 1) showed that pain was more frequent in women ($P < 0.001$), in individuals of White ethnicity ($P = 0.042$), and in those with a self-reported income below the average of their country ($P = 0.002$). Pain more frequently affected MSA-P than MSA-C individuals (95% vs. 82%, $P = 0.015$), but this difference was not retained in the multivariable model.

TABLE 1 *Univariate analysis of the clinical-demographic characteristics of MSA individuals with and without pain based on the patient questionnaire replies*

	No pain n = 24	Pain n = 166	*P*
Demographic features			
Female gender	4 (17)	99 (60)	**<0.001**
Age (y)	63 [54; 71]	62 [55; 69]	>0.950
Age at onset (y)	57 [51; 65]	56 [50; 63]	0.542
Disease duration (y)	5 [3; 6]	5 [4; 8]	0.057
Ethnicity			
White	19 (79)	153 (92)	**0.042**
Other	5 (21)	13 (8)	
Marital status			
Single, widowed, or divorced	4 (17)	34 (20)	0.790
Married/living with a partner	20 (83)	132 (80)	
Presence of a caregiver (n = 18 without pain, n = 148 with pain)	8 (44)	94 (64)	0.130
Education (n = 23 without pain, n = 164 with pain)			
≤10	3 (13)	30 (18)	0.771
>10	20 (87)	134 (82)	
Employment status (n = 21 without pain, n = 164 with pain)			
Retired or unemployed	15 (71)	142 (87)	0.068
Employed full-time or part-time, self-employed	6 (29)	22 (13)	
Annual income (n = 22 without pain, n = 146 with pain)			
Above the average of my country	14 (64)	43 (30)	**0.002**
In line with or below the average of my country	8 (36)	103 (70)	
Continent (n = 19 without pain, n = 158 with pain)			
North America	12 (63)	112 (71)	0.487
Europe	7 (37)	46 (29)	
Clinical features and milestones			
Diagnosis			
MSA-P	3 (13)	62 (37)	**0.034**
MSA-C	18 (75)	80 (48)	
MSA nos	3 (13)	24 (15)	
Bradykinesia	23 (96)	161 (97)	0.560
Ataxia	21 (88)	152 (92)	0.456
Tremor	9 (38)	87 (52)	0.172
Dystonia	5 (21)	92 (55)	**0.002**
Recurrent falls	8 (33)	73 (44)	0.324
Postural deformities	10 (100)	90 (100)	–
Antecollis	4 (17)	51 (31)	0.228
Camptocormia	8 (33)	51 (31)	0.796

(Continues)

TABLE 1 *Continued*

	No pain n = 24	Pain n = 166	*P*
Pisa syndrome	5 (21)	52 (31)	0.294
Orthostatic intolerance	11 (46)	102 (61)	0.145
Bladder problems	17 (71)	136 (82)	0.200
Digestive problems	7 (29)	92 (55)	**0.016**
Swallowing problems	5 (21)	77 (46)	**0.018**
Respiratory problems	3 (13)	60 (36)	**0.021**
Cold hands, cold feet	13 (54)	118 (71)	0.094
Dream-enacting behaviors	13 (54)	93 (56)	0.864
Memory problems	8 (33)	104 (63)	**0.006**
Anxiety or depression (n = 22 without pain, n = 145 with pain)	17 (77)	110 (76)	0.885
Medications			
Total number of medications (n = 184)	3 [0; 5]	5 [3; 8]	**<0.001**
Dopaminergic medication intake	7 (29)	76 (46)	0.125
Effectiveness of dopaminergic medications (n = 7 without pain, n = 74 with pain)	5/7 (71)	51/74 (69)	>0.950
Comorbidities			
Autoimmune	1 (4)	17 (10)	0.478
Cancer	1 (4)	6 (4)	>0.950
Cardiovascular	2 (8)	34 (21)	0.262
Diabetes	0 (0)	13 (8)	0.378
Gastrointestinal	2 (8)	59 (36)	**0.009**
Musculoskeletal	1 (4)	35 (21)	0.052
Neurological	2 (8)	27 (16)	0.542
Polyneuropathy	2 (8)	40 (24)	0.113
Psychiatric	3 (13)	52 (31)	0.089
Respiratory	1 (4)	14 (8)	0.698
EQ-5D-5L			
EQ-5D-5L mobility[a] (n = 23 without pain, n = 145 with pain)	21/23 (91)	141/145 (97)	0.191
EQ-5D-5L self-care[a] (n = 22 without pain, n = 145 with pain)	16/22 (73)	121/145 (83)	0.222
EQ-5D-5L usual activities[a] (n = 23 without pain, n = 145 with pain)	21/22 (96)	143/145 (99)	0.347
EQ-5D-5L pain/discomfort[a] (n = 23 without pain, n = 145 with pain)	7/22 (32)	142/145 (98)	**<0.001**
EQ-5D-5L anxiety/depression[a] (n = 23 without pain, n = 145 with pain)	17/22 (77)	110/145 (76)	0.885
EQ-5D-5L VAS (n = 165)	50 [23; 64]	43 [27; 60]	0.767
EQ-5D-5L index (n = 167)	0.64 [0.48; 0.79]	0.55 [0.39; 0.65]	**0.022**

Qualitative variables are summarized by frequency (percentage) and quantitative variables by median [25th; 75th percentile]. In the case of missing data, the reference sample size for the variable of interest is presented in brackets. Significant *P*-values are presented in bold font.

[a]This frequency (percentage) refers to individuals reporting at least slight problems in the specific EQ-5D-5L subitem.

Abbreviations: EQ-5D-5L, EuroQoL-5 Dimensions-5 Levels; MSA, multiple system atrophy; MSA-P, multiple system atrophy parkinsonian variant; MSA-C, multiple system atrophy cerebellar variant; nos, not otherwise specified; VAS, Visual Analogue Scale.

Pain was associated with dystonia ($P = 0.002$) and digestive ($P = 0.016$), swallowing ($P = 0.018$), respiratory ($P = 0.021$), and memory problems ($P = 0.006$). MSA individuals with pain reported more frequently gastrointestinal comorbidities ($P = 0.009$) and were on a higher number of daily medications ($P < 0.001$).

Multivariable analysis showed that pain remained significantly associated with female gender (odds ratio [OR]: 6.38 [95% CI: 1.27–32.08], $P = 0.025$) and lower income (OR: 5.02 [95% CI: 1.32–19.08], $P = 0.018$; Table 2).

Features Associated with Pain in Different Body Regions

Pain most frequently affected the neck and shoulders (58%), back (45%), and legs (45%). In most patients (73%), several body regions were simultaneously affected, whereas 23% of individuals (n = 44/190) reported diffuse body pain. Pain was most intense in the head, back, abdomen, and feet (Fig. 1). Pain recurred on a daily basis in most body regions and mostly exhibited an episodic-recurrent pattern (Fig. S2). Continuous pain was predominant in individuals with diffuse pain (Fig. S2). Compared to MSA-C, MSA-P individuals reported a higher frequency of pain in the neck and shoulders (72% vs. 49%, $P = 0.003$), arms and legs (48% vs. 27%, $P = 0.006$, and 57% vs. 37%, $P = 0.023$, respectively), hands and feet (35% vs. 20%, $P = 0.034$, and 39% vs. 22%, $P = 0.027$, respectively), and back (57% vs. 37%, $P = 0.011$), and complained more often of diffuse pain (32% vs. 18%, $P = 0.041$). The number of painful body regions was also higher in MSA-P versus MSA-C individuals (4 [2; 6] vs. 3 [1; 4], $P = 0.002$), but no difference was found in the pain VAS, both in general and in the single body regions. Male and female MSA individuals reported comparable frequency and intensity of pain throughout the different body regions, with the exception of diffuse body pain, which was more intense in female individuals (71 [52; 79] vs. 50 [31; 62] than in male MSA individuals on a 100-point pain VAS, $P = 0.002$).

We found that headache was associated with orthostatic intolerance ($P = 0.043$) and neurological comorbidities ($P = 0.001$; Table 3). Neck and shoulder pain showed associations with orthostatic intolerance ($P = 0.002$) and antecollis ($P = 0.001$). Chest pain was significantly associated with orthostatic intolerance ($P = 0.031$) and cognitive problems ($P = 0.014$), whereas abdominal pain was associated with gastrointestinal symptoms ($P < 0.001$) and previously diagnosed gastrointestinal comorbidities ($P = 0.008$). Back pain was associated with musculoskeletal comorbidities ($P = 0.046$). Arm pain was associated with dystonia ($P = 0.028$) and leg pain with dystonia ($P = 0.005$) and musculoskeletal comorbidities ($P = 0.024$). Hand pain showed associations with dystonia ($P = 0.015$), recurrent falls ($P = 0.011$), cognitive problems ($P = 0.006$), musculoskeletal comorbidities ($P = 0.008$), and a self-reported diagnosis of polyneuropathy ($P = 0.035$). Foot pain was associated with a history of polyneuropathy ($P = 0.008$) and joint pain with cognitive problems ($P = 0.007$) and musculoskeletal comorbidities (ie, arthrosis, $P < 0.001$).

TABLE 2 *Binary logistic regression analysis of the clinical-demographic features associated with pain in individuals with MSA*

Clinical-demographic variables	OR [95% CI]	*P*
Female gender	**6.38 [1.27–32.08]**	**0.025**
Disease duration (y)	1.07 [0.82–1.40]	0.626
Ethnicity (other than White)	0.28 [0.05–1.63]	0.157
Presence of a caregiver	3.11 [0.82–11.77]	0.094
Employment status	0.72 [0.17–3.01]	0.651
Annual income in line with or below country average	**5.02 [1.32–19.08]**	**0.018**
Diagnosis		0.449
MSA-C versus MSA-P	0.34 [0.06–1.86]	0.214
MSA nos versus MSA-P	0.34 [0.36–3.19]	0.344

Significant *P*-values are presented in bold font.
Abbreviations: MSA, multiple system atrophy; OR, odds ratio; CI, confidence interval; MSA-C, multiple system atrophy cerebellar variant; MSA-P, multiple system atrophy parkinsonian variant; nos, not otherwise specified.

Pain Management

Seventy-six percent (n = 115/150) of the MSA individuals reporting pain had taken analgesics in the previous 30 days. Nonsteroidal anti-inflammatory drugs (NSAID; n = 49/104, 47%), acetaminophen (n = 41/104, 39%), and opioids (n = 29/104, 28%) were the most frequently used drugs, and approximately every third individual with pain reported combining more classes of drugs (Fig. S3A). Fourteen percent (n = 20/148) of respondents used herbal products against pain. Twenty percent of the survey respondents (n = 29/142) reported that MSA medications (e.g., L-dopa) were adjusted to manage pain. Upon dopaminergic medication adjustment, 57% of them (n = 16/28) reported an improvement, 39% (n = 11/28) no change, and 4% (n = 1/28) a worsening in pain severity.

The most frequent nonpharmacological approaches were physiotherapy (n = 50/152, 33%), massages (n = 45/152, 30%), and heat–cold therapy (n = 46/152, 30%; Fig. S3B). Fifty-seven percent (n = 87/152) of respondents managed their pain without any health-care professional support (Fig. S3C). Pain was otherwise mostly managed by doctors (n = 71/142, 47%),

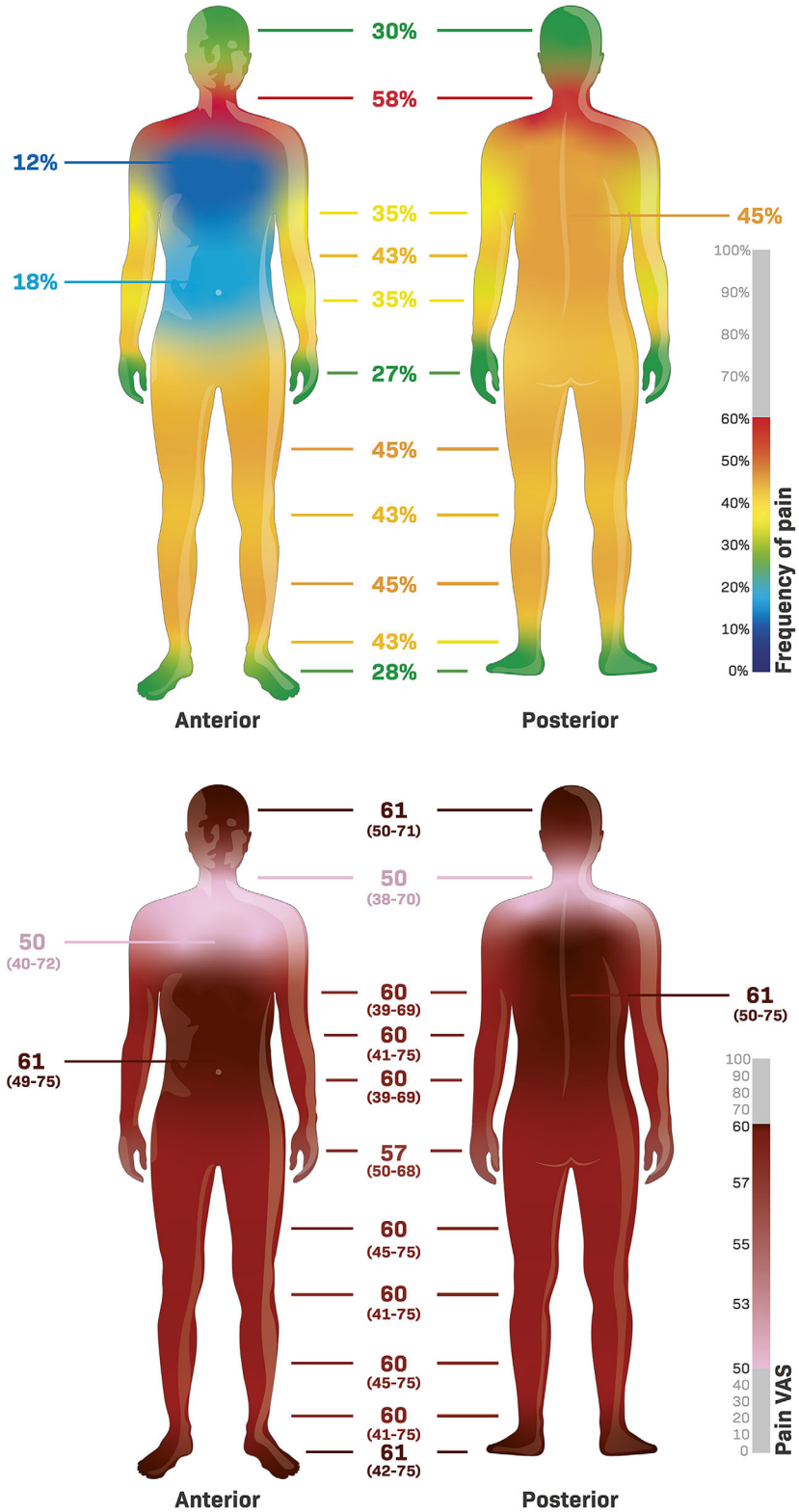

FIG. 1. Frequency (upper panel) and median intensity (VAS [Visual Analog Scale], lower panel) of pain in different body regions as reported by individuals with MSA (multiple system atrophy). Reproduced with permission from biolution GmbH. [Color figure can be viewed at wileyonlinelibrary.com]

especially neurologists (n = 56/71, 79%) and general practitioners (n = 36/71, 51%), with more health-care professionals involved in 26% (n = 39/152) of cases.

Only 53% (n = 78/148) of MSA individuals suffering from pain were at least partially satisfied with their current pain management.

TABLE 3 *Multivariable analysis of the clinical-demographic features and comorbidities associated with pain in each body region*

Outcome variables	OR [95% CI]	*P*	Other (not statistically significant) covariates in the multivariable models
Head			
Orthostatic intolerance	2.15 [1.03–4.49]	0.043	Age, dystonia, cognitive problems
Neurological comorbidities	4.22 [1.76–10.15]	0.001	Age, dystonia, cognitive problems
Neck and shoulders			
Antecollis	4.80 [1.92–12.02]	0.001	Gender, diagnosis, cognitive problems, anxiety or depression, musculoskeletal comorbidities
Orthostatic intolerance	3.24 [1.54–6.82]	0.002	Gender, diagnosis, cognitive problems, anxiety or depression, musculoskeletal comorbidities
Chest			
Orthostatic intolerance	4.11 [1.14–14.80]	0.031	Respiratory problems
Cognitive problems	6.60 [1.46–29.84]	0.014	Respiratory problems
Abdomen			
Gastrointestinal disturbances	13.50 [3.70–49.25]	<0.001	Disease duration
Gastrointestinal comorbidities	3.17 [1.34–7.47]	0.008	Disease duration
Back			
Musculoskeletal comorbidities	2.22 [1.02–4.84]	0.046	Gender, disease duration, diagnosis, postural deformities, orthostatic intolerance
Arms			
Dystonia	2.48 [1.10–5.57]	0.028	Gender, diagnosis
Hands			
Dystonia	2.29 [1.18–4.45]	0.015	Gender, diagnosis
Recurrent falls	2.29 [1.21–4.34]	0.011	Gender, diagnosis
Cognitive problems	3.20 [1.39–7.37]	0.006	Gender, diagnosis
Musculoskeletal	3.39 [1.38–8.32]	0.008	Gender, diagnosis
Polyneuropathy	2.43 [1.07–5.54]	0.035	Gender, diagnosis
Legs			
Dystonia	3.09 [1.40–6.84]	0.005	Disease duration, diagnosis, recurrent falls, polyneuropathy
Musculoskeletal comorbidities	2.68 [1.14–6.23]	0.024	Disease duration, diagnosis, recurrent falls, polyneuropathy
Foot			
Polyneuropathy	3.05 [1.34–6.92]	0.008	Disease duration, cognitive problems, musculoskeletal
Joints			
Cognitive problems	2.47 [1.28–4.75]	0.007	Disease duration
Musculoskeletal comorbidities	5.50 [2.36–12.86]	<0.001	Disease duration

Abbreviations: OR, odds ratio; CI, confidence interval.

Impact of Pain on Daily Activities and Quality of Life

On a 10-point VAS, pain mostly affected household activities (7 [4; 9]), work (7 [4; 9]), and hobbies (7 [4; 8]) of MSA individuals (Fig. S4). Whereas the EQ-5D-5L VAS for the general health status did not differ between MSA individuals with and without pain ($P = 0.767$), the EQ-5D-5L index was lower in those with pain

($P = 0.022$), who scored significantly higher in the EQ-5D-5L pain/discomfort subitem ($P < 0.001$).

Caregiver Responses

Study Population

One hundred seventy-eight informal MSA caregivers signed the informed consent. After data cleaning, questionnaires from 114 caregivers (77 [68%] of alive MSA individuals and 37 [32%] former caregivers of deceased MSA persons) were retained for final analysis (Fig. S1).

The median age of the caregivers was 60 [53; 67] years. Seventy-three percent of them were female, and 68% cared for their spouse/partner. Most caregivers lived in North America (53%), followed by Europe (39%), Oceania (5%), Africa (2%), and South America (1%) (Table S1, S7). The median age of the MSA individuals cared for was 66 [59; 72] years, disease duration was 6 [4; 8] years, and 34% of them were female. Based on information from caregivers, 39% (n = 44/114) of the MSA individuals cared for were diagnosed with MSA-P and 47% (n = 53/144) with MSA-C, and in 15% of patients (n = 17/114) the clinical phenotype was not specified.

MSA-Related Pain Characteristics toward the End of Life

Caregivers of alive and caregivers of deceased MSA individuals reported similar pain prevalence (81%), body distributions, and frequencies ($P = 0.224$) in the persons cared for (Table 4), but pain was more frequently continuous ($P = 0.037$) and more intense in the last year of life of deceased MSA individuals (72 [50; 81] vs. 50 [35; 70] than of alive MSA individuals on the VAS scale, $P = 0.005$) (Table 4). Notwithstanding, the use of painkillers did not differ across deceased individuals in their last year of life and in living individuals with MSA (Table 4).

Impact of the MSA Individual's Pain on Caregiver's Burden and Activities of Daily Living

The EQ-5D-5L index ($P = 0.621$) and the median EQ-5D-5L VAS for the general health status ($P = 0.539$) did not differ across caregivers of MSA individuals with or without pain (Table S1, S7). In caregivers of MSA individuals with pain, the most frequently affected domains of daily living were the caregiver' social activities, hobbies, emotional balance, and overall quality of life (Fig. S4).

Discussion

In our community-based study, 87% of MSA individuals suffered from any kind of pain compared to a 67% pooled pain prevalence found in previous studies.[8,15-25] The frequency of pain observed in our MSA cohort also outnumbered the estimated pain prevalence in the general adult population (21%)[1] and in individuals with chronic neurological conditions (36%),[26] including PD (40%–85%).[27-30] This indicates that MSA individuals may be more susceptible to developing painful sensations compared to other neurological and neurodegenerative disorders.

Previous MSA studies did not find clear sex-related differences in pain prevalence,[8,16,17,20,31] whereas here we observed a higher pain frequency in female MSA individuals. This aligns with observations in the general population and in PD,[32] in which female individuals have a more severe pain burden. Sex-related differences in MSA clinical presentation have been described[33] and, taken together, these observations suggest that both biological and gender-related aspects may contribute to a different susceptibility to pain in female versus male MSA individuals.

We also observed an association between pain and self-reported incomes below the subject country's average. The role of social determinants in pain perception and management is well acknowledged in the bio-psycho-social pain model.[34,35] Health-related costs of and barriers to accessing optimized medical care may also justify this observation.

Former studies reported contrasting results regarding differences in pain prevalence between the MSA-P and MSA-C phenotypes.[19,20,23,31] In our cohort, we found a slightly higher frequency of pain in MSA-P compared to MSA-C, which was not retained in the multivariate model, likely because most MSA individuals, even though classified as suffering from MSA-P or MSA-C, develop a mixed phenotype with disease progression. The frequency of pain in different body regions, as well as the number of painful body regions, was however higher in the respondents with MSA-P compared to MSA-C, suggesting that the bradykinetic-rigid movement disorder or a more pronounced basal ganglia involvement may facilitate the development of painful sensations.

We did not observe any differences in pain prevalence based on age and disease duration, indicating that MSA individuals may develop painful sensations at any time point of their disease journey, but former caregivers of deceased MSA individuals indicated that pain tends to become more intense and continuous toward the end of life. Progressive loss of L-dopa responsiveness, increasing nonmotor symptom burden, and reduced mobility probably account for this observation.

Orthostatic intolerance was significantly associated with neck, shoulder, and chest pain. Coat hanger pain and chest pain are indeed well-recognized symptoms of orthostatic hypotension and should alert clinicians to suboptimal blood pressure control.[36,37] Neck, arm,

TABLE 4 *Univariate comparison of the clinical-demographic characteristics, pain prevalence, and features between MSA individuals in earlier- compared with end-stage disease phases, as reported by MSA caregivers*

	Alive MSA individuals n = 77	Deceased MSA individuals (refers to their last year of life) n = 37	*P*
Demographic features			
Female gender	24 (31)	15 (41)	0.323
Age (y)	65 [60; 72]	67 [59; 74]	0.762
Age at onset (y)	59 [53; 65]	56 [51; 66]	0.310
Disease duration (y)	6 [4; 7]	7 [5; 9]	0.059
Ethnicity			
White	71 (92)	35 (95)	>0.950
Other	6 (8)	2 (5)	
MSA features and milestones			
Diagnosis			
MSA-P	29 (38)	15 (41)	**0.003**
MSA-C	42 (55)	11 (30)	
MSA nos	6 (8)	11 (30)	
Bradykinesia	76 (99)	37 (100)	>0.950
Ataxia	73 (95)	32 (87)	0.123
Tremor	42 (55)	17 (46)	0.390
Dystonia	27 (35)	17 (46)	0.264
Recurrent falls	46 (60)	20 (54)	0.565
Postural deformities	56 (73)	32 (87)	0.101
Antecollis	34 (44)	16 (43)	0.927
Camptocormia	41 (53)	19 (51)	0.849
Pisa syndrome	34 (44)	27 (73)	**0.004**
Orthostatic intolerance	48 (62)	23 (62)	>0.950
Bladder problems	65 (84)	36 (97)	0.058
Digestive problems	38 (49)	22 (60)	0.311
Swallowing problems	49 (64)	31 (84)	**0.028**
Respiratory problems	38 (49)	13 (35)	0.153
Cold hands, cold feet	56 (73)	24 (65)	0.390
Dream-enacting behaviors	53 (69)	28 (76)	0.451
Memory problems	47 (61)	12 (32)	**0.004**
Anxiety or depression (n = 76 without pain, n = 37 with pain)	70 (92)	33 (89)	0.726
Assistive devices			
No assistive devices	9 (12)	1 (3)	**<0.001**
Assistive devices	59 (77)	19 (51)	
Bedridden	9 (12)	17 (46)	

(Continues)

TABLE 4 *Continued*

	Alive MSA individuals n = 77	Deceased MSA individuals (refers to their last year of life) n = 37	*P*
Medications			
Total number of medications	5 [3; 7]	5 [3; 7]	>0.950
Dopaminergic medication intake	37 (48)	27 (73)	**0.012**
Effectiveness of dopaminergic medications (n = 36 without pain, n = 26 with pain)	18 (55)	13 (50)	0.728
Comorbidities			
Autoimmune	3 (4)	1 (3)	>0.950
Cancer	0 (0)	1 (3)	0.325
Cardiovascular	12 (16)	13 (35)	**0.028**
Respiratory diseases	3 (4)	2 (5)	0.659
Diabetes	6 (8)	2 (5)	>0.950
Gastrointestinal	19 (25)	12 (32)	0.383
Musculoskeletal	10 (13)	4 (11)	>0.950
Psychiatric	13 (17)	4 (11)	0.576
Polyneuropathy	11 (14)	6 (16)	0.786
Other neurological conditions	7 (9)	1 (3)	0.272
Pain features			
Pain	62 (81)	30 (81)	>0.950
Head	18 (29)	7 (23)	0.565
Neck and shoulders	38 (61)	20 (67)	0.616
Chest	8 (13)	3 (10)	>0.950
Arms	20 (32)	10 (33)	0.918
Back	28 (45)	16 (53)	0.462
Abdomen	8 (13)	1 (3)	0.262
Hands	15 (24)	8 (27)	0.797
Legs	30 (48)	15 (50)	0.885
Feet	21 (34)	13 (43)	0.378
Joints	23 (37)	7 (23)	0.187
Other	3 (5)	0 (0)	0.548
More body regions	55 (89)	27 (90)	>0.950
Diffuse pain	22 (36)	9 (30)	0.602
Pain frequency (n = 61 without pain, n = 30 with pain)			
Never	2 (3)	0 (0)	0.224
Less than once per week	3 (5)	4 (13)	
Once per week	5 (8)	0 (0)	
Several times per week	23 (38)	9 (30)	

(Continues)

TABLE 4 *Continued*

	Alive MSA individuals n = 77	Deceased MSA individuals (refers to their last year of life) n = 37	*P*
Daily or all the time	28 (46)	17 (57)	
Pain time course (n = 57 without pain, n = 29 with pain)			
Continuous pain	15 (26)	11 (38)	**0.037**
Episodic-recurrent pain	32 (56)	8 (28)	
Continuous pain with pain attacks	10 (18)	10 (35)	
Pain VAS (n = 79)	50 [35; 70]	72 [50; 81]	**0.005**
Pain onset (n = 61 without pain, n = 30 with pain)			
Before the first MSA symptoms	16 (26)	5 (17)	0.440
At the time of the first MSA symptoms	9 (15)	7 (23)	
After the first MSA symptoms	36 (59)	18 (60)	
Pain management			
Professionals involved (n = 53 without pain, n = 29 with pain)			
Doctor	33 (62)	22 (76)	0.210
Nurse	10 (19)	8 (28)	0.362
Chiropractors	3 (6)	1 (3)	>0.950
Acupuncturist	2 (4)	1 (3)	>0.950
Physiotherapist	20 (38)	13 (45)	0.531
Psychologist	3 (6)	3 (10)	0.660
Occupational therapist	11 (21)	12 (41)	**0.047**
More than one professional	30 (57)	23 (79)	0.401
No health-care professional	19 (36)	10 (35)	0.902
Pain treatment			
Use of painkillers (n = 51 without pain, n = 29 with pain)	30/51 (59)	19/29 (66)	0.555

Qualitative variables are summarized by frequency (percentage) and quantitative variables by median [25th; 75th percentile]. In the case of missing data, the reference sample size for the variable of interest is presented in brackets. Significant *P*-values are presented in bold font.
Abbreviations: MSA, multiple system atrophy; MSA-P, multiple system atrophy parkinsonian variant; MSA-C, multiple system atrophy cerebellar variant; nos, not otherwise specified; VAS, Visual Analog Scale.

hand, and leg pain were also associated with other MSA core features like antecollis and dystonia.[38] These findings suggest that, similar to PD, some forms of pain in MSA may be dystonic in nature.[39] These observations have therapeutic implications, indicating that pain in such cases may respond better to improved control of orthostatic hypotension or dystonic features rather than to traditional pain medications.

We further found an association between musculoskeletal comorbidities, gastrointestinal comorbidities, self-reported diagnosis of polyneuropathy, and pain in MSA individuals. Whereas some painful comorbid conditions may simply reflect age-dependent phenomena, others like frozen shoulders, recurrent injurious falls, bowel disturbances, and polyneuropathy may be more directly related to the underlying neurodegenerative process or MSA motor disability, necessitating more specific pharmacological and nonpharmacological treatment strategies.[8]

More than 50% of MSA respondents reported to manage painful symptoms on their own, mostly with NSAIDs and acetaminophen, that are the first-level and least-specific options of the pain treatment ladder. Not surprisingly, only half of MSA respondents were somewhat satisfied with their current pain treatment, and we found that pain negatively influenced core aspects of daily life, such as work and household activities, and the quality-of-life indices of affected MSA individuals.[22,23] This altogether indicates that current MSA pain care standards are far from effective. On the

contrary, we found no difference in the health status of caregivers of MSA individuals with or without pain, suggesting that other MSA clinical milestones, such as losing the ability to walk or eat or sphincter control, may be more critical in affecting the caregivers' health status and burden.[40] However, we found that pain in the MSA person cared for influenced the caregivers' leisure activities and may therefore impact on the caregivers' well-being in the long term.

Strengths and Limitations

Our study has several novel elements. It was the first to investigate pain in MSA individuals using a community-based approach. It also explored the association between pain and multiple socioeconomic factors and its overall impact on daily living and health status of MSA individuals and their caregivers, underscoring the need for improved pain care strategies. The web-based design favored the participation of more disabled individuals and those living in underserved regions, who are often underrepresented in traditional clinic-based studies. Surveying caregivers of deceased MSA individuals further provided mindful insights into end-stage MSA, a disease phase that has been poorly studied so far.

Our study methodology also had drawbacks. Our results were based on self-reported information captured on the REDCap platform, and there was no direct contact with the survey participants. Nonetheless, self-completed questionnaires are recognized to represent useful and valid tools in MSA settings[41] and are increasingly used to explore the personal attitudes, habits, and real-world experiences of individuals living with chronic medical conditions, including pain.[42] After a rigorous data cleaning reflecting the latest MSA diagnostic criteria,[6] the clinical-demographic characteristics of our study cohort also aligned well with published MSA natural history studies, substantiating the robustness of the collected data.[12,38] Compared to historical cohorts, we captured a higher proportion of individuals with MSA-C. This may be in part due to the fact that several survey respondents indicated an undetermined clinical phenotype, and some of them might have been classified as MSA-P on clinical grounds. Despite our explicit invitation to all MSA individuals to take the survey, we cannot exclude that individuals with more severe pain might have been more inclined to engage in the study. In PD, individuals of Black and Asian ethnicity have a higher burden of nonmotor symptoms compared to White individuals.[43] Here we observed a higher frequency of pain in individuals of White ethnicity, but given the high percentage of White respondents in the present study, we were unfortunately unable to closely explore pain differences across MSA individuals with different ethnic backgrounds. The association between pain, anxiety, depression, and lower quality of life is well known in the general population. Here we did not observe any difference in the anxiety, depression, or global health status scores between MSA individuals with and without pain by applying the EQ-5D-5L. This assessment tool was chosen for its brevity and robustness to maximize the survey completion rate. It may, however, show lower sensitivity with respect to other more specific questionnaires (i.e., the MSA-QoL [Multiple System Atrophy Health-Related Quality of Life Scale][44] or the Hospital Anxiety and Depression Scale) in detecting differences in the overall quality of life, anxiety, and depression burden of the examined individuals. The self-reported design also did not enable a differentiation between nociceptive and neuropathic pain types, which would have required a structured clinical assessment. Some respondents might have been on pain modulators like duloxetine or pregabalin to treat other types of symptoms (eg, mood), and this might have influenced the pain threshold in these cases. Nonetheless, the diverse associations found between multiple clinical features, comorbidities, and pain in different body regions call for future adaptations of currently available pain classifications to the multifaceted presentation of MSA.[39,45] Finally, several survey respondents reported pain in multiple body regions and used multiple drugs or a combination of pharmacological and nonpharmacological approaches, preventing an assessment of the satisfaction with single interventions.

Outlook

Our study highlights the prevalence and significant impact of pain as distressing but often overlooked nonmotor feature of MSA. Given its frequency and impact on daily life, future research should focus on understanding the pathophysiological mechanisms underlying pain in MSA, developing disease-specific assessment tools, and formulating targeted therapeutic strategies. It is crucial to recognize that both autonomic dysfunction and motor symptoms may contribute to pain development and exacerbation in MSA, emphasizing the need for multidisciplinary approaches to pain management in this population.

Acknowledgments: This study was supported by a seed grant of Mission MSA (formerly MSA Coalition). N.C., B.C., and F.L. are supported by Mission MSA (formerly MSA Coalition), the Austrian Science Fund (FWF FG 2700), and Dr. Johannes and Hertha Tuba Foundation. The authors declare no relevant conflict of interest related to the present work. The full financial disclosures of all authors are provided at the end of the manuscript. We would like to acknowledge Lalit Kaltenbach for his technical support in the setup and maintenance of the survey on the REDcap platform and biolution GmbH for graphical support in the preparation of Figure 1. We also acknowledge Miss Marta Siha Behrendt, the founder of "Leben mit MSA/Ein Blog," and Ms. Kathy Chapman for their precious contribution to the project purposing and thoughtful feedback on the questionnaire drafts.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Yong RJ, Mullins PM, Bhattacharyya N. Prevalence of chronic pain among adults in the United States. Pain. 2022;163(2):E328–E332. https://doi.org/10.1097/j.pain.0000000000002291
2. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976–1982. https://doi.org/10.1097/j.pain.0000000000001939
3. Nègre-Pagès L, Regragui W, Bouhassira D, Grandjean H, Rascol O. Chronic pain in Parkinson's disease: the cross-sectional French DoPaMiP survey. Mov Disord 2008;23(10):1361–1369. https://doi.org/10.1002/mds.22142
4. Thompson T, Gallop K, Correll CU, et al. Pain perception in Parkinson's disease: a systematic review and meta-analysis of experimental studies. Ageing Res Rev. 2017;35:74–86. https://doi.org/10.1016/j.arr.2017.01.005
5. Fanciulli A, Wenning GK. Multiple-system atrophy. N Engl J Med 2015;372(3):249–263. https://doi.org/10.1056/NEJMra1311488
6. Wenning GK, Stankovic I, Vignatelli L, et al. The Movement Disorder Society criteria for the diagnosis of multiple system atrophy. Mov Disord 2022;37(6):1131–1148. https://doi.org/10.1002/mds.29005
7. Fanciulli A, Stankovic I, Krismer F, Seppi K, Levin J, Wenning GK. Multiple system atrophy. Int Rev Neurobiol 2019;149:137–192. https://doi.org/10.1016/bs.irn.2019.10.004
8. Campese N, Caliò B, Leys F, et al. Pain in multiple system atrophy a systematic review and meta-analysis. Mov Disord Clin Pract 2023;10:1738–1749. https://doi.org/10.1002/mdc3.13897
9. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727–1736. https://doi.org/10.1007/s11136-011-9903-x
10. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208
11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–381. https://doi.org/10.1016/j.jbi.2008.08.010
12. Low PA, Reich SG, Jankovic J, et al. Natural history of multiple system atrophy in the USA: a prospective cohort study. Lancet Neurol. 2015;14(7):710–719. https://doi.org/10.1016/S1474-4422(15)00058-7
13. Wenning GK, Geser F, Krismer F, et al. The natural history of multiple system atrophy: a prospective European cohort study. Lancet Neurol. 2013;12(3):264–274. https://doi.org/10.1016/S1474-4422(12)70327-7
14. Petrovic IN, Ling H, Asi Y, et al. Multiple system atrophy-parkinsonism with slow progression and prolonged survival: a diagnostic catch. Mov Disord 2012;27(9):1186–1190. https://doi.org/10.1002/mds.25115
15. Sung YH, Kang SY. Pain in atypical parkinsonism, vascular parkinsonism, and Parkinson's disease. Neurol Sci 2022;43(8):4797–4802. https://doi.org/10.1007/s10072-022-06035-6
16. You HY, Wu L, Yang HT, Yang C, Ding XL. A comparison of pain between Parkinson's disease and multiple system atrophy: a clinical cross-sectional survey. Pain Res Manag. 2019;2019:3150306. https://doi.org/10.1155/2019/3150306
17. Ory-Magne F, Pellaprat J, Harroch E, et al. Abnormal pain perception in patients with multiple system atrophy. Parkinsonism Relat Disord. 2018;48:28–33. https://doi.org/10.1016/j.parkreldis.2017.12.001
18. Yust-Katz S, Hershkovitz R, Gurevich T, Djaldetti R. Pain in extrapyramidal neurodegenerative diseases. Clin J Pain 2017;33(7):635–639. https://doi.org/10.1097/AJP.0000000000000437
19. Zhang LY, Cao B, Ou RW, et al. Non-motor symptoms and the quality of life in multiple system atrophy with different subtypes. Parkinsonism Relat Disord. 2017;35:63–68. https://doi.org/10.1016/j.parkreldis.2016.12.007
20. Kass-Iliyya L, Kobylecki C, Mcdonald KR, Gerhard A, Silverdale MA. Pain in multiple system atrophy and progressive supranuclear palsy compared to Parkinson's disease. Brain Behav. 2015;5(5):e00320. https://doi.org/10.1002/brb3.320
21. Colosimo C, Morgante L, Antonini A, et al. Non-motor symptoms in atypical and secondary parkinsonism: the PRIAMO study. J Neurol. 2010;257(1):5–14. https://doi.org/10.1007/s00415-009-5255-7
22. Schrag A, Sheikh S, Quinn NP, et al. A comparison of depression, anxiety, and health status in patients with progressive supranuclear palsy and multiple system atrophy. Mov Disord 2010;25(8):1077–1081. https://doi.org/10.1002/mds.22794
23. Schrag A, Geser F, StampferKountchev M, et al. Health-related quality of life in multiple system atrophy. Mov Disord 2006;21(6):809–815. https://doi.org/10.1002/mds.20808
24. Calvert M, Pall H, Hoppitt T, Eaton B, Savill E, Sackley C. Health-related quality of life and supportive care in patients with rare long-term neurological conditions. Qual Life Res 2013;22(6):1231–1238. https://doi.org/10.1007/s11136-012-0269-5
25. Higginson IJ, Gao W, Saleem TZ, et al. Symptoms and quality of life in late stage Parkinson syndromes: a longitudinal community study of predictive factors. PLoS One. 2012;7(11):e46327. https://doi.org/10.1371/journal.pone.0046327
26. Cragg JJ, Warner FM, Shupler MS, Jutzeler CR, Cashman N, Whitehurst DGT, Kramer JK. Prevalence of chronic pain among individuals with neurological conditions. Health Rep 2018;29(3):11–16.
27. Broen MPG, Braaksma MM, Patijn J, Weber WEJ. Prevalence of pain in Parkinson's disease: a systematic review using the modified QUADAS tool. Mov Disord 2012;27(4):480–484. https://doi.org/10.1002/mds.24054
28. Buhmann C, Wrobel N, Grashorn W, et al. Pain in Parkinson disease: a cross-sectional survey of its prevalence, specifics, and therapy. J Neurol. 2017;264(4):758–769. https://doi.org/10.1007/s00415-017-8426-y
29. Brefel-Courbon C, Grolleau S, Thalamas C, et al. Comparison of chronic analgesic drugs prevalence in Parkinson's disease, other chronic diseases and the general population. Pain. 2009;141(1):14–18. https://doi.org/10.1016/j.pain.2008.04.026
30. Beiske AG, Loge JH, Rønningen A, Svensson E. Pain in Parkinson's disease: prevalence and characteristics. Pain. 2009;141(1):173–177. https://doi.org/10.1016/j.pain.2008.12.004
31. Xiao Y, Zhang L, Wei Q, et al. Health-related quality of life in patients with multiple system atrophy using the EQ-5D-5L. Brain Behav. 2022;12(10):e2774. https://doi.org/10.1002/brb3.2774
32. Martinez-Martin P, Falup Pecurariu C, Odin P, et al. Gender-related differences in the burden of non-motor symptoms in Parkinson's disease. J Neurol. 2012;259(8):1639–1647. https://doi.org/10.1007/s00415-011-6392-3
33. Leys F, Eschlböck S, Campese N, et al. Sex-related differences in the clinical presentation of multiple system atrophy. Clin Auton Res 2024;34(2):253–268. https://doi.org/10.1007/s10286-024-01028-1
34. Meints SM, Edwards RR. Evaluating psychosocial contributions to chronic pain outcomes. Prog Neuropsychopharmacol Biol Psychiatry. 2018;87:168–182. https://doi.org/10.1016/j.pnpbp.2018.01.017
35. Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth. 2019;123(2):e273–e283. https://doi.org/10.1016/j.bja.2019.03.023
36. Mathias CJ, Mallipeddi R, Bleasdale-Barr K. Symptoms associated with orthostatic hypotension in pure autonomic failure and multiple system atrophy. J Neurol. 1999;246(10):893–898. https://doi.org/10.1007/s004150050479

37. Gibbons CH, Freeman R. Orthostatic dyspnea: a neglected symptom of orthostatic hypotension. Clin Auton Res 2005;15(1):40–44. https://doi.org/10.1007/s10286-005-0227-1

38. Köllensperger M, Geser F, Ndayisaba J, et al. Presentation, diagnosis, and management of multiple system atrophy in Europe: final analysis of the European multiple system atrophy registry. Mov Disord 2010;25(15):2604–2612. https://doi.org/10.1002/mds.23192

39. Wasner G, Deuschl G. Pains in Parkinson disease-many syndromes under one umbrella. Nat Rev Neurol. 2012;8(5):284–294. https://doi.org/10.1038/nrneurol.2012.54

40. Cheong JLY, Goh ZHK, Schrag A. Support needs of people with multiple system atrophy. Parkinsonism Relat Disord. 2024;120:106019. https://doi.org/10.1016/j.parkreldis.2024.106019

41. Palma JA, Krismer F, Meissner WG, et al. Patient-reported symptoms in the global multiple system atrophy registry. Mov Disord Clin Pract. 2022;9(7):967–971. https://doi.org/10.1002/mdc3.13544

42. Gewandter JS, Edwards RR, Hill KP, et al. Cannabinoid therapy. Clin J Pain. 2023;39(6):249–258. https://doi.org/10.1097/AJP.0000000000001109

43. Sauerbier A, Schrag A, Brown R, et al. Clinical non-motor phenotyping of black and Asian minority ethnic compared to white individuals with Parkinson's disease living in the United Kingdom. J Parkinsons Dis. 2021;11(1):299–307. https://doi.org/10.3233/JPD-202218

44. Schrag A, Selai C, Mathias C, et al. Measuring health-related quality of life in MSA: the MSA-QoL. Mov Disord. 2007;22(16):2332–2338. https://doi.org/10.1002/mds.21649

45. Chaudhuri KR, Rizos A, Trenkwalder C, et al. King's Parkinson's disease pain scale, the first scale for pain in PD: an international validation. Mov Disord 2015;30(12):1623–1631. https://doi.org/10.1002/mds.26270

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

SGML and CITI Use Only
DO NOT PRINT

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.

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

Full financial disclosures of all authors for the preceding 12 months

N.C. has nothing to disclose.

G.G. has nothing to disclose.

J.W. reports speaker fees and honoraria for advisory boards from Argenx, Amicus, and Sanofi outside of the present work.

A.S. has nothing to disclose.

B.C. has nothing to disclose.

F.L. has nothing to disclose.

P.B. has nothing to disclose.

L.K. has nothing to disclose.

L.Z. reports honoraria from Novartis and a research grant from EVTZ/Austrian Science Fund (FWF): IPN 135-B outside of the present work.

K.B. has nothing to disclose.

K.R.C. has nothing to disclose.

A.S. has nothing to disclose.

R.F. has nothing to disclose.

H.K. is editor in chief of *Clinical Autonomic Research*, published by Springer-Nature, and serves as principal investigator of studies sponsored by Biogen MA Inc. (TRACK MSA, S19-01846) and Vaxxinity Inc. (UB-312, S22-01332). He has received consultant fees from Takeda Pharmaceutical Company Ltd, Ono Pharma UK Ltd, Theravance Biopharma US Inc, and Parexel. He receives royalties from Up To Date. He receives research support from NIH-NINDS, the U.S. Food & Drug Administration, the Familial Dysautonomia Foundation, and the HSAN IV Foundation.

R.G. has nothing to disclose.

S.K. is supported by the excellence initiative VASCage (Research Centre on Vascular Ageing and Stroke, project number 898252) of the Austrian Research Promotion Agency FFG (COMET program—Competence Centers for Excellent Technologies) funded by the Federal Ministry for Climate Protection, Environment, Energy, Transport, Innovation and Technology; the Federal Ministry for Labour and Economy; and the federal states Tyrol (via Standortagentur), Salzburg, and Vienna (via Vienna Business Agency).

W.P. has nothing to disclose.

K.S. has nothing to disclose.

G.W. reported consultancy and lecture fees from Inhibicase, Ono, and Theravance and research grants from the FWF-Austrian Science Fund, Mission MSA (formerly MSA Coalition), Parkinson Fonds Austria, and Dr Johannes and Hertha Tuba Foundation outside of the present work.

A.F. reports royalties from Springer Verlag; speaker fees and honoraria from Theravance Biopharma, GE Health Care, Broadview Ventures, the Austrian Autonomic Society, and Elsevier; and research grants from the FWF-Austrian Science Fund, the Medical University of Innsbruck, Mission MSA (formerly MSA Coalition), Dr Johannes and Hertha Tuba Foundation, and the Austrian Exchange Program outside of the present work.