

A Cross-Sectional Study on Drug Use in Multiple System Atrophy

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Abstract

Background Drug use has rarely been studied in multiple system atrophy (MSA) while such patients receive many treatments based on weak evidence.

Objective To analyze drug use from the database of the French MSA Reference Center, and to compare it with data from patients with Parkinson disease (PD).

Methods Medication of 147 MSA and 180 age- and sex-matched PD patients was analyzed. Motor and autonomic symptoms were explored in MSA patients by the SCOPA-Autonomic and Unified MSA Rating Scale (UMSARS).

Results MSA and PD patients received a mean of five different drugs. MSA patients were more frequently exposed to laxatives, antidiabetic medications, antihypotensives, muscarinic antagonists, alpha-adrenergic blockers, and antidepressants. Levodopa consumption was less in MSA-C (cerebellar) patients compared with MSA-P (parkinsonian) and PD patients. Dopamine agonists were more consumed by PD than MSA patients. MSA patients with more severe disability received more laxatives, anticoagulants, and antidepressants. MSA-P patients received more analgesics. “Probable” MSA patients received more antihypotensives and less alpha-adrenergic blockers. Patients with higher SCOPA-Autonomic scores were more frequently on antihypotensives or antidepressants. Drug associations leading to potential adverse interactions were uncommon (usually <5 %).

Conclusions Some differences in drug use between MSA and PD patients were observed and expected, including those used for the relief of parkinsonian motor symptoms, autonomic dysfunction, and depression. Many of these drugs are frequently used in MSA in the absence of well-established, positive, benefit-risk evaluations, thus calling for better assessments. The reason why other medications, including anti-diabetic medications, were more consumed by MSA patients remains unclear and deserves further exploration.

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Key points

Multiple system atrophy (MSA) is an orphan disease with only a few specifically approved treatments available, leading to frequent empirical off-label drug use.

In this study, drug use was compared between MSA and Parkinson Disease (PD) patients and related to MSA characteristics.

Significant differences were observed in drug use patterns between MSA and PD patients and in relation to PD characteristics.

While some findings were expected given the clinical features of MSA patients, others were more puzzling and may highlight some topics related to patient management and disease pathophysiology that are worthy of further research.

1 Introduction

Multiple system atrophy (MSA) is a relentlessly progressive, rare neurodegenerative disorder [1]. Only a few symptomatic treatments are currently available with limited efficacy [2].

Drug use, which is defined by the World Health Organization (WHO) as the marketing, distribution, prescription, and use of drugs with special emphasis on the resulting medical, social, and economic consequences [3], has been seldom analyzed in MSA, especially in large series. The interest in evaluating drug use is that it allows the assessment of therapeutic and adverse effects of a given drug as well as medical or non-medical aspects of drug prescription and its appropriateness [3]. These issues are especially relevant in MSA as the paucity of approved treatments causes frequent off-label drug use.

Here, we performed a drug use analysis using the MSA reference center database, and compared it with a sample of PD patients serving as a reference group. As secondary objectives, we compared drug use according to MSA characteristics and patients' demographics.

2 Methods

2.1 Sample

Data of 147 consecutive patients that were recorded between 2008 and 2011 in the Registry of the French Reference Center for MSA were analyzed. The French MSA Reference

Center was created in 2007 by the French Ministry of Health [4] to facilitate the management of patients suffering from such a disorder and to facilitate research in this field [5]. A prospective database including demographics, clinical characteristics, and treatments of all patients referred to and followed up by the reference center was created and is available. All patients gave informed written consent before entering the database. Data include an evaluation with the Unified MSA Rating Scale (UMSARS) [6] and the SCOPA-Autonomic scale [7, 8]. MSA patients were classified as MSA-P (P for parkinsonian) or MSA-C (C for cerebellar) subtype and "probable" or "possible" MSA according to current consensus criteria [9].

To better characterize drug use in MSA, a comparison with PD was performed, as this disorder is better studied and usually drugs with acknowledged efficacy and safety are used. Data on PD patients were obtained from another database [10]. PD patients were managed within the same movement disorders units and recruited in the same period. PD patients were selected to match by age and sex the MSA sample. Patients were included if they fulfilled the UK PD Society Brain Bank criteria for PD [11] and had neither undergone neurosurgical interventions for PD nor cognitive impairment preventing data collection in a reliable manner. All patients gave informed consent allowing their data to be registered in the databases used in this study.

2.2 Drug Use Assessment

All medications were systematically collected from all patients and coded according to the WHO Anatomical Therapeutic Chemical (WHO-ATC) classification system [12]. Only medications taken by more than 5 % of MSA patients were retained for further analysis.

Doses of antiparkinsonian drugs were also retrieved. Levodopa daily equivalent dose was calculated according to the usual formula [13].

The summary of product characteristics of medications most frequently consumed by MSA patients was reviewed to identify possible sources of drug-drug interactions. We focused on drugs whose co-administration might lead to reduced efficacy of one or both drugs, or to adverse events. The following potential sources of interactions were identified:

1. co-administration of laxative drugs with muscarinic antagonists, serotonergic antidepressants, amantadine, opioids, monoamine oxidase B (MAO-B) inhibitors, and entacapone, potentially leading to reduced efficacy of laxatives,
2. co-administration of alpha-adrenoreceptor agonists (i.e., midodrine) with alpha-antagonists leading to reduced efficacy of the former,

3. co-administration of drugs for orthostatic hypotension (midodrine, fludrocortisone) with dopamine agonists, antihypertensives, or any antidepressant, leading to reduced efficacy of the former,
4. co-administration of MAO-B inhibitors with antidepressants or opioids, leading to serotonergic syndrome.

2.3 Multiple System Atrophy (MSA) and Parkinson Disease (PD) Clinical Evaluation

The severity of PD was evaluated by means of the Unified PD Rating Scale (UPDRS) parts II + III (II: Activities of daily living and III: Motor examination) score [14].

To compare symptom severity between PD and MSA patients, UMSARS I + II and UPDRS II + III scores were expressed as a percentage of the maximal possible score, which are 104 for the UMSARS or 160 for the UPDRS.

Disease duration in both patient groups was assessed as the time since the diagnosis.

2.4 Statistical Analysis

This was designed as an exploratory drug-use cross-sectional study. The frequency of drug use was first compared between MSA and PD patients by a chi-square test. Alpha-error inflation due to multiple comparisons was controlled by means of the Holms step-down procedure [15]. A power analysis showed that 150 MSA and 180 PD patients would allow the detection of differences in drug use of 10–15 % with 80 % power and an alpha error of 5 %.

In second place, drug use within MSA patients was related to demographic data and disease characteristics. Patients' age, SCOPA-Autonomic, and UMSARS total

scores were dichotomized to their medians, which were 66 years, 22 points, and 47 points, respectively. Chi-square tests were used to identify differences in drug use between these groups as well as in gender, MSA clinical type (P vs. C), and diagnostic certitude ("possible" vs. "probable"). Holms step-down procedure was used to control for alpha-error inflation.

Finally, the frequency of patients with drug co-administration leading to potential interaction was explored, without any further comparison.

Data were analyzed by IBM SPSS Statistics version 20 (New York, USA). Alpha was set at 0.05. Data are expressed as mean \pm standard error of the mean.

3 Results

Patients' characteristics are shown in Table 1. Briefly, no differences were found in age or gender. As expected, MSA patients had shorter disease duration but more severe disability than PD patients.

3.1 Drug Use in MSA and PD Patients

No differences were found in the number of medications consumed by PD or MSA patients (Table 1).

Details about drug consumption according to the WHO-ATC classification system in MSA and PD patients are shown in Table 2. MSA patients consumed more frequently drugs for autonomic symptoms, including constipation (laxatives), orthostatic hypotension (midodrine, fludrocortisone), urinary dysfunction (muscarinic antagonists, alpha-adrenergic blockers), diabetes mellitus, and depression as compared with PD patients. Conversely,

Table 1 Patient characteristics

	PD (<i>n</i> = 180)	MSA (<i>n</i> = 147)
Age (years)	66.7 \pm 0.8	65.4 \pm 0.7
Male, <i>n</i> (%)	102 (57)	73 (50)
Disease duration (years)	8.8 \pm 0.4	5.1 \pm 0.2**
UPDRS 2 + 3 (points)	36.9 \pm 1.4	–
UMSARS 1 + 2 (points)	–	49.0 \pm 1.3
Disease severity (% of maximal score) ^a	23.1 \pm 0.9	47.1 \pm 1.2**
SCOPA-Autonomic (points)	–	23.7 \pm 0.8
MSA type, <i>n</i> (%)		
Cerebellar	–	56 (38)
Parkinsonism	–	90 (62)
Diagnostic certitude, <i>n</i> (%)		
Possible	–	27 (18)
Probable	–	119 (82)
Number of medications consumed (\pm SD)	5.0 \pm 0.2	5.1 \pm 0.2

MSA multiple system atrophy, PD Parkinson disease, SD standard deviation, UPDRS Unified PD Rating Scale, UMSARS Unified MSA Rating Scale

** *p* < 0.01

^a UPDRS II + III and UMSARS I + II scores were expressed as a percentage of the maximal possible score (160 or 104 respectively), to allow for direct comparisons

Table 2 Medication use in MSA and PD patients

WHO-ATC categories	PD (n = 180) n (%)	MSA (n = 147) n (%)
Alimentary tract and metabolism		
Antacids	23 (13)	30 (21)
Laxatives	19 (11)	28 (19)*
Domperidone	39 (22)	35 (24)
Drugs for diabetes mellitus	5 (3)	16 (11)*
Vitamins and minerals	10 (6)	13 (9)
Blood and blood-forming organs		
Antithrombotics	19 (11)	29 (20)
Cardiovascular system		
Cardiac therapy	11 (6)	10 (7)
Midodrine	8 (4)	48 (33)**
Fludrocortisone	2 (1)	14 (10)**
Any antihypertensive	54 (30)	32 (22)
Cholesterol-lowering drugs	16 (9)	17 (12)
Genito-urinary system		
Muscarinic antagonists	7 (4)	27 (18)**
Alpha-adrenergic blockers	5 (3)	11 (8)*
Hormones		
Levothyroxine	13 (7)	14 (10)
Nervous system		
Analgesics	25 (14)	19 (13)
Any antiparkinsonian medication	180 (100)	107 (73)**
Anti-muscarinics	10 (6)	1 (1)*
Levodopa	157 (87)	98 (67)**
Amantadine	30 (17)	17 (12)
Dopamine agonists	147 (82)	31 (21)**
MAO-B inhibitors	13 (7)	5 (3)
Entacapone	41 (23)	21 (14)
Antipsychotics	6 (3)	0 (0)
Benzodiazepines/anxiolytics/hypnotics	39 (22)	35 (24)
Any antidepressant	46 (26)	71 (49)**
Imipraminics	5 (3 %)	3 (2)
SSRIs	27 (15)	40 (27)*
Other antidepressants	14 (8)	30 (21)**
Respiratory		
Drugs for respiratory conditions	3 (2)	7 (5)

Only drugs consumed by more than 5 % of MSA patients were analyzed

MAO-B monoamine oxidase B, MSA multiple system atrophy, PD Parkinson disease, SSRIs selective serotonin reuptake inhibitors, WHO-ATC World Health Organization-Anatomical Therapeutic Chemical

* $p < 0.05$, ** $p < 0.01$ (Chi-square test with Holms step-down alpha-error adjustment procedure). The category "Other antidepressants" includes venlafaxine, tianeptine, mianserine, duloxetine, and mirtazapine

antiparkinsonian drugs were less frequently consumed by MSA than PD patients.

3.2 Drug Use in MSA Patients According to Demographics and Disease Characteristics

Older MSA patients were more frequently treated with anticoagulants (11 vs. 2 %, $p < 0.04$), hypno-anxiolytics (33 vs. 16 %, $p < 0.05$), and antidepressants of mixed mechanism (28 vs. 14 %, $p < 0.05$) as compared with younger MSA patients.

Male patients consumed more frequently drugs for diabetes than female patients (19 vs. 3 %, $p < 0.001$). The same applied to drugs for urinary dysfunction such as muscarinic antagonists (27 vs. 9 %, $p < 0.001$) and alpha-adrenergic blockers (27 vs. 0 %, $p < 0.001$).

Patients with longer MSA duration (>5 years) received more frequently alpha-adrenergic blockers (14 vs. 3 %, $p < 0.05$).

MSA patients with SCOPA-Autonomic scores >22 were more frequently exposed to fludrocortisone (18 vs. 3 %, $p < 0.05$) and antidepressants (57 vs. 41 %, $p < 0.05$).

Table 3 Drugs used for the treatment of motor symptoms in PD and MSA-P or MSA-C patients

	PD (<i>n</i> = 180) <i>n</i> (%)	MSA-P (<i>n</i> = 90) <i>n</i> (%)	MSA-C (<i>n</i> = 56) <i>n</i> (%)	<i>p</i> -value
Parkinsonian syndrome				
Any antiparkinsonian medication	180 (100)	81 (90)	26 (46) ^{a,b}	0.001
Antimuscarinics	10 (6)	1 (1) ^a	0 (0) ^a	0.05
Levodopa	157 (87)	79 (88)	19 (34) ^{a,b}	0.001
Levodopa daily dose ^c	701 ± 33	724 ± 41	347 ± 42 ^{a,b}	0.001
Dopamine agonists	147 (82)	26 (29) ^a	5 (9) ^{a,b}	0.001
MAO-B inhibitors	13 (7)	4 (4)	1 (2)	0.3
Entacapone	41 (23)	21 (23)	0 (0)	0.001
Levodopa equivalent daily dose ^c	1,225 ± 98	851 ± 52 ^a	369 ± 49 ^a	0.001
Cerebellar ataxia				
Vitamin E	0 (0)	1 (1)	5 (9) ^{a,b}	0.001
Buspirone	1 (1)	0 (0)	2 (4)	0.05
Riluzole	0 (0)	0 (0)	0 (0)	–
Acetazolamide	0 (0)	0 (0)	0 (0)	–
Antiepileptic drugs	19 (11)	12 (13)	5 (9)	0.7
Physostigmine	0 (0)	0 (0)	0 (0)	–
Trimethoprim-sulfamethoxazole	0 (0)	0 (0)	0 (0)	–
Spasticity				
Baclofen	0 (0)	0 (0)	1 (2)	0.1

MAO-B monoamine oxidase B, MSA-C multiple system atrophy (cerebellar), MSA-P multiple system atrophy (parkinsonian), PD Parkinson disease

^a $p < 0.05$ vs. PD, ^b $p < 0.05$ vs. MSA-P (analysis of variance followed by Bonferroni test or Chi-square test followed by z test for proportions with Bonferroni adjustment)

^c Patients not receiving either levodopa or other antiparkinsonian medications were not included in the calculation of levodopa dose or levodopa-equivalent daily dose, respectively

Patients with UMSARS I + II scores >47 received more frequently laxatives (30 vs. 10 %, $p < 0.05$), anticoagulants (10 vs. 2 %, $p < 0.04$), and antidepressants (61 vs. 38 %, $p < 0.05$).

Patients with MSA-P were more frequently exposed to antihypertensive (28 vs. 12 %, $p < 0.05$) and analgesic (19 vs. 4 %, $p < 0.05$) medications as compared with patients with MSA-C.

Finally, patients with a diagnosis of “probable” MSA were more frequently exposed to drugs for orthostatic hypotension than those with “possible” MSA (43 vs. 15 %, $p < 0.05$) and less frequently to alpha-adrenergic antagonists (5 vs. 19 %, $p < 0.05$).

The use of antiparkinsonian medications was compared between PD, MSA-P, and MSA-C patients (Table 3). Overall, MSA-C patients consumed less antiparkinsonian medications than PD and MSA-P patients. MSA-P patients consumed less dopamine agonists than PD patients and hence, the levodopa daily equivalent dose was lower. Conversely, no differences were found between PD and MSA-P patients in the frequency of exposure to at least one antiparkinsonian medication, to

levodopa and in levodopa daily dose. MSA-C patients were more frequently on drugs used for off-label treatment of ataxia, such as vitamin E or buspirone.

3.3 Frequency of Co-administration of Drugs Leading to Potential Interactions in MSA Patients

Laxatives were co-administered with muscarinic antagonists in four subjects (3 %), serotonergic antidepressants in six (4 %), amantadine in three (3 %), opioids in five (4 %), MAO-B inhibitors in one (<1 %), and entacapone in four (3 %).

No patient received alpha-adrenoreceptor agonists and antagonists at the same time.

Co-administration of drugs for orthostatic hypertension with antihypertensives was found in six subjects (3 %), with dopamine agonists in five (3 %) and with antidepressants in 28 (19 %).

Co-administration of MAO-B inhibitors with antidepressants was observed in three (2 %) patients and none with opioids.

4 Discussion

MSA is an orphan disease with only a few specifically approved treatments available, leading to frequent empirical off-label drug use. There is nearly no information about drug prescription and consumption in this disease, apart from small anecdotal retrospective reports and a recent survey reporting neuropsychiatric drug consumption in a sample of European patients [16]. Our data were collected systematically, in almost 150 consecutive patients fulfilling international diagnostic criteria for the diagnosis of MSA recruited prospectively, which conforms to a unique dataset. There are however some methodological limitations with this study: (1) our data were restricted to French centers, (2) measures of disease severity and autonomic function were used as proxy indicators in a cross-sectional analysis, but no assessment of consequences and causality could be performed, thus making possible some bias, (3) no measures of drug efficacy and safety were available, (4) comorbidities were not registered, (5) the control group of PD patients was extracted from another survey that had been conducted at the same time by the same centers and investigators, but had not been specifically pre-planned to serve as a comparative group, and (6) the sample size only allowed the analysis of drugs consumed by more than 5 % of the studied patients, and between-group differences <10 % may have been missed because of insufficient power.

Nonetheless, our data provide novel findings in a nearly “empty” area. Quantitatively, we found that MSA patients consumed a mean of five different drugs. This number was comparable to that recorded in PD patients of the same age but with less severe disability. There were many qualitative differences between the MSA and PD groups, including consumption of drugs for symptoms related to nervous, cardiovascular, genito-urinary, alimentary, and metabolic systems. Some of these findings were expected according to the clinical features of MSA and PD. Others were less expected, including the consumption of antidepressants and anti-diabetic medications.

As anticipated, antiparkinsonian medications were less consumed by MSA than PD patients, although three-quarters of the former received at least one antiparkinsonian drug, which is not trivial considering that such treatments have limited efficacy in MSA. The most plausible explanation for this difference is that there are two different phenotypes in MSA; MSA-C with prominent cerebellar ataxia and minor parkinsonian symptoms, at least in early disease, as opposed to MSA-P with predominant parkinsonism. Another possible explanation is that parkinsonian motor symptoms are less dopa-responsive in MSA than PD. This difference is indeed a key diagnostic criterion to separate both disorders clinically [17]. Poor symptomatic control

may explain why fewer MSA patients take antiparkinsonian therapies in the long term compared with PD patients. However, we observed that MSA-P patients had comparable levels of levodopa consumption (frequency of exposure and mean daily dose) than PD patients. This result may illustrate the fact that prescribers tried pushing the dose of levodopa as much as possible in MSA-P patients, in the absence of better therapeutic alternatives. This might not necessarily be an optimal strategy, because unnecessary high doses of levodopa may offer a questionable motor benefit for a greater risk of side effects. The fact that MSA-P patients used less dopamine agonists than PD patients is in line with this hypothesis, as it is conceivable that prescribers may have preferred using levodopa in MSA-P patients for its rapid and potent motor effects, as opposed to dopamine agonists exhibiting weaker antiparkinsonian potency and greater risk of orthostatic hypotension and other cardiovascular adverse reactions [18], especially in patients with autonomic failure. Overall, these results on antiparkinsonian treatment consumption are consistent with the findings of the European Multiple System Atrophy Registry [16].

As opposed to dopaminergic medications for the management of parkinsonian symptoms, an objective demonstration of drug efficacy for the treatment of cerebellar ataxia is weak [19]. Drugs such as vitamin E or buspirone are listed among those that have been considered to provide some benefit for ataxia. In line with this concept, we found these two drugs to be more commonly consumed by MSA-C patients than MSA-P and PD patients. However, only 10 % of patients received these medications, suggesting a limited use in clinical practice.

Drugs for autonomic dysfunction, including midodrine and fludrocortisone for orthostatic hypotension, laxatives for constipation, and muscarinic antagonists for urinary tract dysfunction, were more frequently used in MSA than PD patients, especially by those with a diagnosis of “probable” MSA. This is consistent with the severe autonomic dysfunction that is a hallmark of MSA [1, 9, 20]. However, such prescriptions were reported in only 20–30 % of the MSA population, while the presence of autonomic dysfunction is a mandatory criterion for the diagnosis of MSA. It is likely that all dysautonomic symptoms were not severe enough to require drug therapy or that physicians considered that patients would not likely benefit from such treatments or wanted to avoid drug-drug interactions, which will be revisited in the next paragraphs. Exposure to alpha-adrenergic blockers was also more frequent in MSA patients. Alpha-adrenergic blockers may have some appropriate indication in urinary tract dysfunction in MSA [21], as they may reduce post-micturition residuals [22]. Nonetheless, alpha-blockers are also known to aggravate orthostatic hypotension [22], because of their

vasodilating effects generating cardiovascular adverse reactions and limiting their utility in MSA. The use of muscarinic antagonists for urinary urgency should be reserved to patients with detrusor hyperreflexia [23]. Poor detrusor contractility, a frequent feature in later stages of MSA [24], reduces the efficacy of these drugs and carries the risk for elevated post-micturition residuals. Taken together these data highlight the complexity of the treatment of autonomic dysfunction in MSA.

MSA patients were more frequently exposed to antidepressants than PD patients. The proportion of treated patients was not trivial, as one out of two patients was exposed. This may be explained by the large prevalence of depressive symptoms in MSA patients, possibly owing to the rapid and severe disability characterizing this disorder [25]. In turn, more severe depression might translate into more frequent utilization of antidepressants, as was herein observed. Notwithstanding, it should be emphasized that both parkinsonian and autonomic symptoms have been reported as a consequence of imipraminic and non-imipraminic antidepressant prescriptions [26, 27]. Therefore, the risk/benefit ratio of this drug class should again be better and more carefully revisited before using these drugs too broadly in MSA patients.

A more intriguing finding was that MSA patients were more frequently exposed to antidiabetic drugs as compared with PD patients. Interestingly, recent studies have shown that diabetes may contribute to neurodegeneration, and may represent a risk factor for PD [28]. Our results may thus be interpreted as an indication that diabetes may be an equally or even stronger risk factor for MSA, which has been suggested by previous studies [29].

Older and more severely affected MSA patients were more frequently exposed to anticoagulants. This may be explained because of greater motor disability and immobility, which is one of the main features of MSA [24] and is also more frequent in the elderly. According to such a scenario, prescribers may have prescribed anticoagulants to prevent or treat immobility-related thrombosis [30]. However, balance and falls are a major problem in MSA patients, and the benefit-risk ratio of such medications that increase the risk of post-traumatic hematoma deserves once more a more careful evaluation. Finally, analgesics were more frequently prescribed in MSA-P compared with MSA-C patients, probably because pain due to rigidity and postural deformities is more frequent in the former [31].

In this study, we had the opportunity to explore drug associations with the potential of negative drug-drug interactions. Drug interactions can be the cause of many hospital admissions [32]. They are associated with more than 20 % of reported adverse reactions and with therapeutic failure or reduced efficacy [32]. We observed in a few patients some “illogical” associations, including for

example the co-prescription of laxatives and drugs causing constipation (antimuscarinics, opiates, amantadine) or the concomitant consumption of drugs to treat hypertension and hypotension. However, such cases were rare (<5 % of the patients) and in some instances might have been justified, as most dysautonomic MSA patients have both daytime orthostatic hypotension and night-time supine hypertension [33]. We observed quite commonly the co-administration of drugs for orthostatic hypotension and antidepressants (19 % of MSA cases). This association may induce cardiovascular concerns [27] and calls for caution, while alternative treatments are currently not available. Finally, we recorded three cases of co-prescription of a serotonin reuptake inhibitor with a MAO-B inhibitor, exposing the patients to the risk of serotonin syndrome. Such an association is theoretically prohibited, especially considering the poor level of evidence documenting their individual usefulness in MSA.

5 Conclusion

Significant differences in drug consumption between MSA and PD patients were observed. While some findings were expected given the clinical features of MSA patients, others were more puzzling and may highlight some topics related to patient management and disease pathophysiology that are worthy of further research. Drug associations potentially leading to adverse interactions were infrequent. Large registries, such as those of the French MSA Reference Center are needed to better assess and optimize drug therapy in MSA patients.

Conflict of interest MVR, SPL, APL, WM, and FT do not have any conflicts of interest to disclose in relation to this study. OR has acted as an advisor for many pharmaceutical companies developing treatments for MSA. No funding was received for the conduct of this study.

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