



Current Management and Emerging Therapies in Multiple System Atrophy

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Abstract

Multiple system atrophy (MSA) is a progressive neurodegenerative disease variably associated with motor, nonmotor, and autonomic symptoms, resulting from putaminal and cerebellar degeneration and associated with glial cytoplasmic inclusions enriched with α -synuclein in oligodendrocytes and neurons. Although symptomatic treatment of MSA can provide significant improvements in quality of life, the benefit is often partial, limited by adverse effects, and fails to treat the underlying cause. Consistent with the multisystem nature of the disease and evidence that motor symptoms, autonomic failure, and depression drive patient assessments of quality of life, treatment is best achieved through a coordinated multidisciplinary approach driven by the patient's priorities and goals of care. Research into disease-modifying therapies is ongoing with a particular focus on synuclein-targeted therapies among others. This review focuses on both current management and emerging therapies for this devastating disease.

Key Words Multiple system atrophy · multidisciplinary care · α -synuclein · symptomatic therapy · disease-modifying

Introduction

Multiple system atrophy (MSA) is a rare, progressive neurodegenerative disease with estimated incidence of 0.6 to 0.7 cases per 100,000 person-years and prevalence of 3.4 to 4.9 cases per 100,000 [1–4]. The mean age of symptom onset is reported between 54 and 63 years, depending on the study, and the estimated survival from symptom onset is 6 to 11 years (median survival, ~9.5 years) [5–8]. MSA comprises a variable combination of autonomic dysfunction, parkinsonism, and ataxia, with the predominance of one or other motor syndrome defining parkinsonian (MSA-P) or cerebellar subtypes (MSA-C) [9]. Currently available lab tests or imaging do not

provide additional diagnostic or prognostic sensitivity or specificity beyond that of a thorough clinical assessment. Some fluid biomarkers and imaging findings, however, are thought to be supportive [10, 11]. Commensurate with the multisystem nature of the disease, effective management requires both evidence-based and off-label multidisciplinary treatment with the patient at the center of an interdisciplinary team of well-coordinated providers including the neurologist, consulting physicians, rehabilitation therapists (physical, occupational, and speech–language), dietician, social worker, and potential research staff. Such treatment is driven largely by personalized, symptomatic management of the patient's specific constellation of symptoms. There are currently no approved disease-modifying therapies, although research in a variety of mechanistically driven areas is ongoing and the patient should be given the opportunity to participate in clinical trials. This article provides an overview of the pathology and pathogenesis, clinical presentation, evaluation, treatment, and management, including both evidence-based and off-label therapies. We also discuss ongoing research efforts to develop potential symptomatic and disease-modifying therapies for this complex and devastating disease.

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Pathology and Pathogenesis

Neuropathologically, MSA exhibits putaminal, pontine, and cerebellar atrophy [12] that is associated with shared and differing relative patterns of degeneration consistent with the specific clinical subtype. MSA-P is typically associated with prominent caudal putamen and caudate involvement with preferential degeneration of GABAergic medium spiny neurons, as well as substantia nigra involvement with degeneration of dopaminergic striatonigral neurons [13, 14]. In contrast, MSA-C tends to show more prominent degeneration of the dentate and inferior olivary nuclei, as well as the basis pontis, cerebellar vermis and hemispheres, and cerebellopontine fibers [13]. Both subtypes share involvement of the motor and supplementary motor cortex. The pathology of the locus coeruleus and vagus and Onuf's nuclei, and degeneration of the intermediolateral spinal columns, contribute to autonomic dysfunction [15, 16].

MSA histopathology is characterized by oligodendroglial cytoplasmic inclusions (GCIs), or Papp–Lantos bodies, that contain abundant pathologic α -synuclein aggregates and other proteins (Fig. 1) [13, 17–20]. Similar neuronal inclusions have also been described in the cytoplasm (NCIs) and nuclei (NNIs), but are much less common [17, 21]. GCI pathology is a defining feature of “definite” MSA and correlates with neuronal loss and disease duration [22]. Neuronal loss, axonal degeneration, astrogliosis, and microglial activation are widespread and variably involve the putamen, substantia nigra, pons, inferior olivary nucleus, cerebellum, and brainstem depending on the MSA subtype [23].

The presence of α -synuclein aggregates in oligodendrocyte is a notable distinguishing feature of MSA pathology as compared to other synucleinopathies, such as Parkinson disease and dementia with Lewy bodies, in which α -synuclein deposits are predominantly neuronal. The physiological role of α -synuclein remains an active area of research, and evidence suggests roles in synaptic vesicular function and

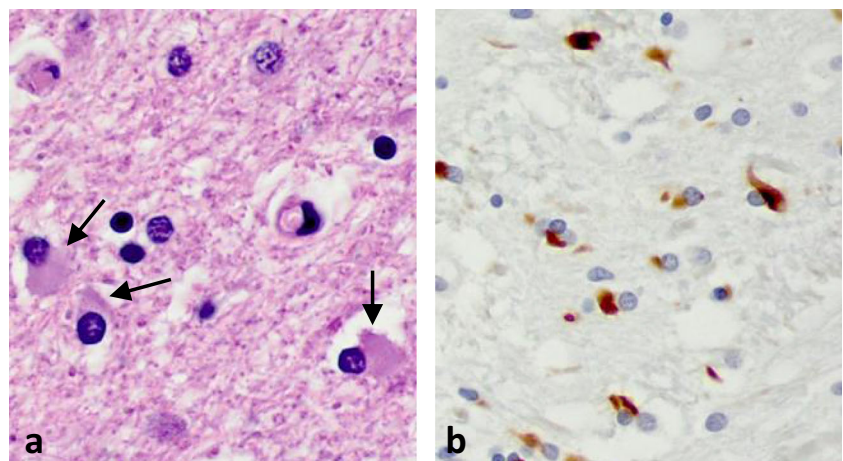
neurotransmitter release [24]. The role of α -synuclein in glial cells has yet to be elucidated. Pathologically, α -synuclein is phosphorylated and self-aggregates to form fibrils, aggregates, and larger intracellular inclusions recognized as Lewy bodies [25]. A wealth of evidence indicates that pathological forms of α -synuclein (i.e., fibrils or aggregates) are secreted or released from neurons, extracellularly, and may propagate α -synuclein pathology from cell to cell in a prion-like fashion [26–28]. Further evidence suggests the presence of different conformational “strains” of α -synuclein fibrils that result in preferential degeneration of certain cell types and provide an explanation for the clinical diversity among synucleinopathies [29, 30]. Human brain homogenates from MSA patients have been shown to “seed” pathological α -synuclein fibrils in cultured cells and neuronal deposits in transgenic mice expressing human α -synuclein [31, 32]. Although different α -synuclein “strains” have been shown to target distinct cellular populations and cell types within the brain, and recapitulate some of the selective targeting observed in human synucleinopathies, a major limitation of these models is that they exhibit only neuronal α -synuclein pathology. Understanding how or why α -synuclein pathology targets mainly oligodendrocytes has yet to be elucidated. Nevertheless, these findings have led to significant efforts toward disease-modifying therapies focused on reduction or clearance of pathological α -synuclein [33].

Clinical Symptoms

Motor Symptoms

Historically, a variety of eponymous or general anatomic terms have been used to refer to MSA, often denoting the predominant constellation of symptoms. These terms included Shy–Drager syndrome, striatonigral degeneration, and olivopontocerebellar atrophy, which tended to refer to patients

Fig. 1 (A) Glial cytoplasmic inclusions (arrows) in oligodendrocytes (hematoxylin and eosin stain). (B) α -Synuclein staining (brown) in GCIs



with predominant autonomic dysfunction, parkinsonism features, or cerebellar dysfunction, respectively. The discovery that these seemingly different syndromes shared a common pathology of oligodendroglial cytoplasmic inclusions (GCI) motivated efforts to modernize terminology. The first consensus definition was established in 1998 and revised in 2007 [34, 35].

The core motor symptoms of MSA are parkinsonism and ataxia. Modern categorization includes 2 subtypes: the MSA-parkinsonism subtype (MSA-P) with predominant symptoms of tremor, rigidity, and bradykinesia that are poorly responsive to levodopa and the MSA-cerebellar subtype (MSA-C) with predominant symptoms of gait and limb ataxia, scanning dysarthria, and cerebellar oculomotor dysfunction, though parkinsonian features are sometimes also present. Generally, symptom presentation is more symmetric and tremor less prominent compared to that in Parkinson disease. MSA tremor has been described as having a higher frequency and lower amplitude as compared to Parkinson disease, with a “jerky,” stimulus-sensitive, myoclonic component in the setting of sustained posture holding, referred to as polyminimyoclonus [36, 37]. Initial presenting symptoms of MSA vary widely and overlap with those of other parkinsonian disorders and sporadic adult-onset ataxias. As such, delay in diagnosis and misdiagnosis are common [38–40].

Beyond the core motor symptoms of MSA, a variety of additional motor symptoms are common. Dystonia affects over 40% of patients [41] and includes limb, orofacial, cervical, and truncal dystonias. Limb dystonias can lead to significant disability, painful contractures, and early striatal hands or toe deformities. Anterocollis, Pisa syndrome, and camptocormia, characterized by abnormal forward or lateral flexion of the trunk during standing or walking that is relieved by lying down, are particularly associated with MSA, although these can be seen in other forms of parkinsonism [42, 43]. In addition, restless leg syndrome (RLS) has been described as affecting between 5 and 30% of patients [44, 45]. Other suggestive features include hyperreflexia, Babinski sign, early dysarthria, dysphagia, inspiratory sigh, and stridor [9]. The speech in MSA in particular is characterized by a mixed, spastic–hypokinetic (or ataxia, if MSA-C) dysarthria, sometimes with a vocal “quiver” or “flutter” [46, 47]. Dysphagia occurs earlier and is more severe than that seen in Parkinson disease.

Nonmotor, Cognitive, and Affective Symptoms

MSA has significant cognitive and affective symptoms, often referred to as “nonmotor” symptoms, many of which play a prominent role in patients’ quality of life and should be a major focus of clinical assessment and therapy [48]. Although dementia is an exclusion criterion for a clinical diagnosis of MSA, single or multidomain cognitive impairment

is not uncommon and frank dementia is reported in up to 10 to 15% of patients [49]. Executive dysfunction is most common and consistent with frontal–subcortical pathology seen in MSA and other parkinsonian disorders.

Depressive symptoms and anxiety are common in MSA and more prevalent and severe than in Parkinson disease, and correlate with poor quality of life [50–54]. Emotional lability or pseudobulbar affect, characterized by uncontrolled, sudden, inappropriate laughter or crying, may also occur [55].

Autonomic Symptoms

Prominent autonomic symptoms are a key defining feature of MSA, but have variable presentations. The clinical criteria for MSA require the presence of either orthostatic hypotension or significant urinary dysfunction such as urgency, increased frequency, incontinence, or retention (needing catheterization) with erectile dysfunction in males that is not otherwise explained by diseases such as diabetes or autonomic neuropathy [35]. It is important to note that significant orthostatic hypotension may be lacking in a given patient despite the presence of other prominent autonomic symptoms. Additional autonomic features may include gastrointestinal symptoms such as gastroparesis, constipation, or diarrhea; heat and cold intolerance; flushing, diaphoresis, hypohidrosis, or global anhidrosis; and acrocyanosis characterized by bluish discoloration of the fingers or toes [4, 56, 57]. Urinary dysfunction, in particular, is a prominent and common early autonomic symptom in MSA with incomplete bladder emptying, urinary retention, and other voiding difficulties [58, 59]. In males, erectile dysfunction can be a telltale sign of early MSA even in the absence (i.e., preceding) of orthostatic symptoms [60, 61].

Autonomic symptoms are the earliest symptom in up to 50% of patients with early or severe autonomic dysfunction carrying a more guarded prognosis [62, 63]. Clinicians should rule out secondary causes of dysautonomia such as diabetes or other common maladies such as benign prostatic hypertrophy (BPH) in males or bladder prolapse in females that may contribute to urinary dysfunction. In addition, primary autonomic failure (PAF) should only be entertained as an alternative diagnosis after 5 years of isolated autonomic disturbances as some patients with presumptive PAF diagnosis will phenoconvert to MSA in time [64]. As olfactory function is relatively preserved in PAF compared to PD and MSA, this may be a clinically useful distinguishing feature [65].

Sleep Issues and Disordered Breathing

A variety of sleep-related problems are common in MSA. REM sleep behavior disorder (RBD), characterized by recurrent dream enactment with excessive motor behavior (i.e., thrashing, punching, kicking) [66], is frequent not only in MSA but other α -synucleinopathies, Parkinson disease, and

dementia with Lewy bodies, with over 90% of patients affected [4]. RBD contributes to poor sleep quality and, if severe, may result in injury to self or bedpartners. RBD symptoms may precede the onset of MSA by several years and “burn-out” later in disease [67]. Central and obstructive sleep apnea are also common in MSA [68, 69]. Laryngeal stridor [70, 71] is a particularly concerning symptom that may play a central role in survival through oxygen desaturations, respiratory failure, and sudden death during sleep [69]. Stridor may be a presenting feature of MSA and is defined as a strained, high-pitched, harsh respiratory sound, mainly inspiratory, occurring only during sleep or during both sleep and wakefulness, that is caused by laryngeal dysfunction leading to narrowing of the rima glottides [70]. Diagnosis can be made clinically if present or with the aid of a recording or bed partner, and confirmed through laryngoscopy, sleep endoscopy, or video polysomnography. Given the prevalence of these symptoms, polysomnography should be considered in the initial workup for patients with MSA even in the absence of reported symptoms.

Diagnosis

The diagnosis of MSA is primarily clinical and based on the most recent consensus criteria [35]. Three levels of diagnostic certainty were established: definite, probable, and possible (Table 1). Whereas a diagnosis of definite MSA requires post-mortem histopathologic confirmation, probable MSA requires autonomic failure (orthostatic hypotension defined by a drop of 30 mmHg systolic and 15 mmHg diastolic from supine to within 3 min of standing, or urinary incontinence/retention and erectile dysfunction in males) and either parkinsonism that is poorly levodopa-responsive or a predominant cerebellar syndrome. Possible MSA includes less stringent criteria: parkinsonism or cerebellar syndrome plus at least one feature suggesting autonomic dysfunction (i.e., urinary urgency, frequency, or incomplete emptying; erectile dysfunction in men, or orthostatic hypotension, though only requiring a 20-point drop in systolic and a 10-point drop in diastolic blood pressure). At least one additional feature is required such as hyperreflexia/Babinski sign or stridor, or imaging findings consistent with MSA such as putaminal atrophy, FDG–PET hypometabolism, or evidence of striatal presynaptic dopaminergic denervation on SPECT or PET. With the 2008 revised criteria, improved sensitivity was achieved in early disease for the “probable MSA” category [72]. It should be noted, however, that despite the criteria’s > 90% sensitivity in late disease and the relative improvement in early probable disease, sensitivity remains low at 41%, warranting continued efforts to improve diagnosis for early disease [72].

Despite an aggressive effort to identify reliable diagnostic biomarkers for MSA, to date there are no approved serum or

cerebral spinal fluid-based tests to aid clinical diagnosis or to assess disease progression. Neuroimaging remains a primary diagnostic modality and is often helpful. Supportive findings on brain imaging include MRI- or CT-based evidence of pontine and/or cerebellar atrophy (Fig. 2). In MSA-C, there is predominant olivopontocerebellar atrophy, with loss of pontocerebellar fibers and gliosis best seen on T2-weighted MRI imaging, sometimes producing the characteristic “hot cross bun” sign [11]. In MSA-parkinsonism, MRI may show evidence of putaminal atrophy with decreased T2 signal in the posterior putamen and a hyperintense T2 rim, also known as a putaminal rim sign [73], which is typically observed at 1.5-T MRI strength but is unreliable with the more commonly used 3-T scanners today. These findings correlate with increased free-water [74, 75] and iron deposition within the putamen (as seen on MRI susceptibility-weighted imaging) [76, 77]. In addition, FDG–PET has been shown to help with MSA diagnosis and shows hypometabolism of the putamen, pons, and cerebellum [78]. Dopamine transporter (DAT) PET and SPECT imaging, although not specific for MSA, shows reduced striatal binding consistent with presynaptic dopaminergic denervation [79].

Cardiac sympathetic neuroimaging may also help distinguish MSA from Parkinson disease. In a meta-analysis, cardiac iodine-123 meta-iodobenzylguanidine (MIBG) scintigraphy showed high sensitivity and specificity for distinguishing PD from other forms of parkinsonism [80]. MSA patients are usually found to have normal cardiac postganglionic sympathetic innervation, although a third of patients have some degree of cardiac sympathetic denervation [81, 82]. By contrast, Parkinson disease patients have altered sympathetic denervation in virtually all cases [83–86]. As a result, a normal MIBG scan can reliably exclude PD but not MSA [84, 85]. Additional diagnostic studies may include olfactory testing, autonomic test such as tilt table and sweat tests (e.g., QSART), urodynamic testing, and anal sphincter EMG and manometry, as well as gastric emptying and polysomnography.

Despite a lack of clinically reliable diagnostic biopsy-based or body fluid biomarkers, several investigational biomarkers have shown potential value and a combination of biomarkers may provide increased sensitivity and specificity [10]. A recent meta-analysis suggests that a combination of α -synuclein, neurofilament light chain (NFL), and total tau may have diagnostic value. A reduction of α -synuclein and an increase in NFL in CSF has the potential to distinguish MSA patients from PD and healthy controls [10]. In addition, a reduction of total tau (t-tau) in CSF may distinguish MSA from healthy controls, and an elevation of t-tau could distinguish MSA from PD. Additional CSF biomarkers under study include uric acid, homocysteine, phosphorylated tau, and coenzyme Q10. Investigational CSF biomarkers also include microRNAs (miRNAs), with recent data suggesting that a combination of

Table 1 Clinical diagnostic criteria for MSA

MSA	Parkinsonism (MSA-P)	Cerebellar syndrome (MSA-C)	Autonomic symptoms
A sporadic progressive, adult (> 30 years)-onset disease characterized by:			
Definite	Pathology proven: widespread α -synuclein inclusions in glial cytoplasm with evidence of neurodegeneration in olivopontocerebellar or striatonigral structures		
Probable	Poorly levodopa-responsive parkinsonism (bradykinesia with tremor, rigidity, or postural instability)	Cerebellar syndrome: - Gait ataxia with... - Cerebellar dysarthria - Limb ataxia, or - Oculomotor dysfunction (e.g., hyper/hypometric saccades, nystagmus)	<i>and...</i> Urinary incontinence or retention with erectile dysfunction in males, or orthostatic hypotension (OH: drop in BP within 3 min of standing of \geq 30 mmHg systolic or 15 mmHg diastolic)
Possible	Parkinsonism <i>and 1 of the following:</i> - Rapidly progressive parkinsonism - Poor levodopa response - Postural instability \leq 3 years of motor onset - Dysphagia \leq 5 years onset - Hyperreflexia with Babinski - Stridor - Cerebellar features Imaging: - MRI finding of atrophy of the putamen, pons, MCP, or cerebellum - FDG-PET hypometabolism in the putamen, brainstem, or cerebellum	Cerebellar dysfunction <i>and 1 of the following:</i> - Hyperreflexia with Babinski - Stridor - Parkinsonism Imaging: - MRI finding of atrophy of the putamen, pons, MCP, or cerebellum - Presynaptic nigrostriatal dopaminergic denervation on PET or SPECT (e.g., DaTscan)	<i>and...</i> Urinary urgency, frequency, incomplete bladder emptying, ED in males, or orthostatic hypotension (OH: drop in BP within 3 min of standing of \geq 20 mmHg systolic or 10 mmHg diastolic)

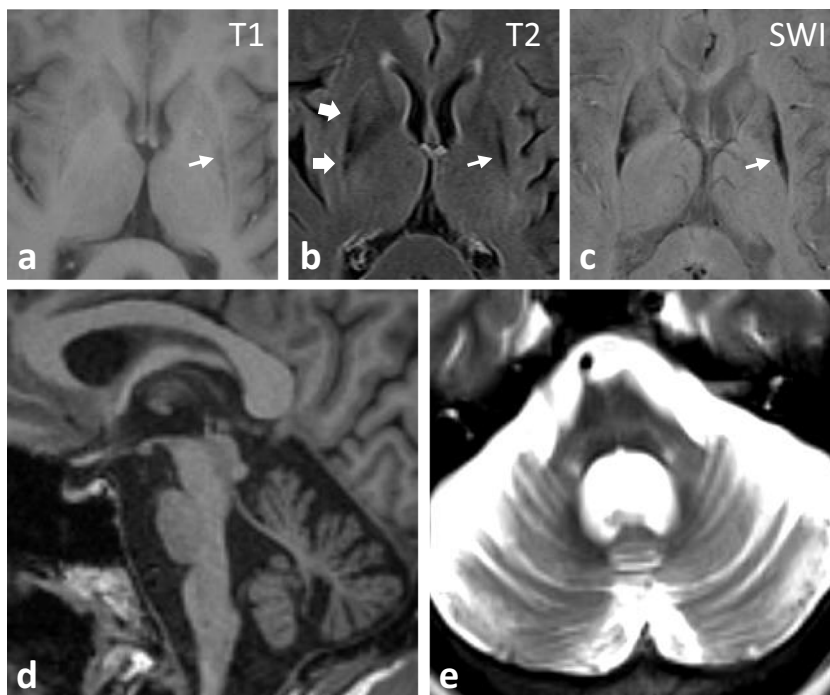
Modified from the Second Consensus Criteria for the Clinical Diagnosis of Multiple System Atrophy [19]

increased expression of miR-19a, miR-19b, miR-24, and miR-34c was able to distinguish MSA patients from healthy controls [87]. In addition, serum and plasma have been investigated for potential biomarkers. Another meta-analysis found

increased plasma α -synuclein among PD patients which may have value in MSA patients as well [88].

Finally, skin biopsy has shown promise as a potential investigational biomarker. Evidence suggests that cutaneous α -

Fig. 2 MRI brain imaging in MSA-P (A–C) demonstrates putaminal atrophy (small arrow) with hypointense T1/T2 signal and hyperintense T2 rim sign (large arrows). (C) SWI shows hemosiderin dense posterior putamen. (D) Olivopontocerebellar atrophy in MSA-C. (E) T2 image with pontine atrophy, gliosis, and “hot cross bun” sign



synuclein deposition in unmyelinated somatosensory fibers of the subepidermal plexus, but not in dermal autonomic fibers, can distinguish MSA from other subtypes of synucleinopathy [89]. In addition, several recent studies utilizing the ultrasensitive real-time quaking induced conversion (RT-QuIC) assay claim the ability to detect α -synuclein aggregation in tissues such as olfactory mucosa [90] and the submandibular gland [91] with high sensitivity and specificity for α -synucleinopathies including Parkinson disease and MSA.

Symptomatic Management

To date there are no approved disease-modifying therapies for MSA; thus, treatment is focused mainly on symptom management tailored to the specific patient (Table 2) and importantly involves a multidisciplinary approach with rehab and other allied healthcare partners. As a multisystem disorder, MSA often requires care from several disciplines including neurology, cardiology, gastroenterology, urology, sleep medicine, pulmonary, psychiatry, neuropsychology, dietary, palliative care, and hospice. Social services and support are critical and should include engaging social work, care partners, and discussion of life goals, end-of-life planning, and advanced directives.

While ideal, multidisciplinary care for MSA and other neurodegenerative disorders faces challenges in delivery. Current care models are often plagued by a lack of patient-centered care with poor continuity and delayed or reactive care delivery [92, 93]. Two multidisciplinary models, the Canadian and Dutch models, have been evaluated for clinical effectiveness [94, 95]. Although both models show benefit, the Canadian model appears more robust, although no universal standard has yet been recognized [96]. More recent work has focused on expanding and standardizing the Canadian Chronic Care Model (CCM) for patients with chronic neurologic conditions including parkinsonian disorders for the purposes of objective evaluation and standardization, but this remains a developing area in need of further study [97–100]. It is important to note that much of this work has focused on dementia and Parkinson disease, with the presumption that atypical parkinsonism would similarly benefit. Such a presumption, however, remains an untested hypothesis.

Parkinsonism

Tremor, rigidity, bradykinesia, and postural instability are core features of MSA-P and are observed irrespective of subtype in nearly 90% of cases [2]. A poor or unstained response to levodopa is common and among the core diagnostic features of MSA, helping to differentiate MSA-P from Parkinson disease [35, 101]. Nearly a third of MSA-P patients benefit from levodopa therapy, but temporarily with mean duration of

3.5 years in one study [6]. Levodopa remains a first-line therapy with trial up to 2 g total daily dose of levodopa (titrated from 100 to 300 mg 3–4 times daily) recommended for at least 3 months [102]. Clinically significant improvement is characterized as 30% decrease in the Unified Multiple System Atrophy Rating Scale (UMSARS) [101]. Levodopa may worsen orthostatic hypotension or cause other more severe side effects less common among Parkinson disease patients. Reports of deterioration with withdrawal of the medication even in the context of apparent nonresponse are common and may justify continuation of treatment [4].

Dopamine agonists may be used as a second choice, but lack supporting evidence and are generally not preferred because of their increased side effect profile relative to levodopa [61, 102]. Amantadine, up to 300 mg in 3 divided doses, is a reasonable alternative treatment option (including as an add-on), though there are no controlled studies to date [2, 103, 104].

Nonpharmacological approaches such as physical, occupational, and speech therapy are both complementary and essential therapies in MSA. Randomized controlled trials support occupational therapy in mild to moderate MSA [105], and although there are no such trials supporting physical therapy in MSA specifically, given the strength of the evidence for the motor symptoms of Parkinson disease [106], the assumption is that parkinsonian MSA symptoms will similarly benefit.

Deep brain stimulation for parkinsonism in MSA is not recommended as symptoms often poorly respond and rapidly progress relative to Parkinson disease. Case studies and series suggest it is ineffective and, as a result, should not be considered a therapeutic option [107–109].

Dystonia and Spasticity

Focal dystonia such as anterocollis or blepharospasm is a common feature of MSA with prevalence reported between 12 and 46% [16, 41]. Medical therapies for dystonia including benzodiazepines and anticholinergics are not commonly used because of cognitive and respiratory risks. As is true with other causes of dystonia, botulinum toxin injections can be quite effective for dystonic symptoms in MSA, especially for blepharospasm and limb dystonia [110]. Treatment of cervical dystonia, in particular anterocollis, may confer substantial risk because of the potential for exacerbating underlying dysphagia often associated with disease, and abundant caution is advised [111].

Ataxia

There are currently no medications available that provide evidence-supported improvement in ataxic symptoms in MSA. Similar to parkinsonism, however, evidence supports intensive physical therapy for gait, balance, and overall

Table 2 Symptomatic therapies in MSA

Symptom	Pharmacologic therapy	Nonpharmacologic therapy
Parkinsonism	Carbidopa/levodopa commonly to 200 to 300 mg × 3-4 times daily, 2000 mg daily max Amantadine up to 100 mg × 3 times daily	Physical therapy (PT) Occupational therapy (OT) Regular activity, exercise
Dystonia	Trihexyphenidyl, botulinum toxin	PT and OT
Spasticity	Muscle relaxants (e.g., baclofen, tizanidine) Botulinum toxin	PT and OT
Dysarthria	—	Speech therapy
Dysphagia	—	SLP swallow evaluation, therapy
Autonomic failure		
Orthostatic hypotension	Fludrocortisone 0.1-0.4 mg daily Midodrine 2.5 to 10 mg × 3 times daily Droxidopa 100 to 600 mg × 3 times daily Pyridostigmine 60 mg × 3 times daily Atomoxetine 18 mg daily Caffeine	Hydration, fluid intake Increased dietary salt Abdominal binders Waist-high compression stockings
Postprandial hypotension	Octreotide 25–50 mcg before meals Acarbose 25–50 mg before meals	Eat smaller, more frequent meals Avoid high-carbohydrate meals Avoid alcohol Remain seated (or lie down) after eating
Supine hypertension	Nightly clonidine 0.1-0.3 mg Hydralazine 25-50 mg, minoxidil 2.5 mg Losartan 25 mg Nifedipine 10-20 mg Nitroglycerin TD (wipe off in AM) Sildenafil 25 mg	Assess scheduled medications Elevate head of bed Bedtime snack (postprandial effect)
Urge incontinence	Solifenacin, trospium Mirabegron	Timed urination Intermittent self-catheterization
Incomplete bladder emptying	Tamsulosin 0.4 mg daily Prazosin 0.5-1 mg twice daily	Suprapubic catheter placement
Sialorrhea	Botulinum toxin	Sugar-free lozenges, gum Papaya or grape seed extract
Nocturia	Desmopressin 0.2-0.6 mg nightly	No fluids 3-4 h before bed
Constipation	Stool softeners Senna, laxatives, enemas Polyethylene glycol 3350 Magnesium citrate Linaclotide Lubiprostone	Increased fluid, fiber intake Activity/exercise
Erectile dysfunction	Sildenafil 50-100 mg pm Tadalafil 5-20 mg pm Vardenafil 5-20 mg pm Apomorphine subq injections Prostaglandin E1 or papaverine intercavernous injections	Implants
Sleep disorders		
REM-behavior disorder	Melatonin extended release 3-15 mg nightly Clonazepam 0.25-2 mg nightly	
Restless leg syndrome (or RLS/PLMS)	Dopamine agonists: Pramipexole 0.125-0.5 mg, ropinirole 0.25-4 mg, or rotigotine TD 2-6 mg/24 h Gabapentin <i>versus</i> gabapentin enacarbil	
Nocturnal stridor	Benzodiazepines (i.e., clonazepam)—relative contraindication in sleep apnea Botulinum toxin injection (dystonic stridor)* Minimally invasive procedures**†	First line—ventilation with CPAP Persistent/severe—consider tracheostomy
Sleep apnea	—	Change in sleep position, weight loss Oral appliance therapy CPAP <i>versus</i> AutoPAP (if central) Uvulopalatopharyngoplasty Neurostimulation

Table 2 (continued)

Symptom	Pharmacologic therapy	Nonpharmacologic therapy
Neuropsychiatric symptoms		
Depression	SSRIs/SNRIs	Psychotherapy
Anxiety	Anxiolytics, benzodiazepines Buspirone	Cognitive behavioral therapy
Pseudobulbar affect	Dextromethorphan/quinidine	

* Insufficient evidence to support treatment

† E.g., airway dilation, arytenoidectomy, cordectomy

coordination, as well as speech therapy for ataxic dysarthria [112–116].

Sleep Disturbance

Sleep disorders are common in MSA and include insomnia, daytime somnolence, restless legs syndrome (RLS), REM sleep behavior disorder (RBD), and sleep disordered breathing [117]. Up to 71% of MSA patients report insomnia and have problems falling or staying asleep, or early morning awakenings. The causes are multifactorial and include nocturnal discomfort (due to rigidity or dystonia), urinary dysfunction (e.g., nocturia), anxiety and depression, and other parasomnias [118]. Good sleep hygiene is important and include maintaining consistent bed and wake times (avoid also prolonged in-bed time) and avoiding caffeine and excessive daytime naps. For those who get out of bed or are unable to fall asleep, having a planned relaxing activity such as reading a book, listening to music, or a warm bath can help. Consider also a referral to psychology for brief behavioral therapy. Treat anxiety and depression, if present. If discomfort is causing sleep difficulty, inquire about specific symptoms such as rigidity, dystonia, RLS, or tremors and treat accordingly. Mild pain relievers may be necessary and appropriate for some patients.

Daytime sleepiness is a frequent complaint and may lead to naps or more problematic “sleep attacks” that interfere with meals. Factors that contribute to fatigue and excessive daytime somnolence include sleep deprivation (from insomnia), sleep disordered breathing, circadian rhythm disruption, and drug side effects (e.g., pain medications, benzodiazepines, and change in dopaminergic medications). A baseline sleep study can help check for other sleep disorders such as sleep apnea, RBD, RLS, or periodic limb movements in sleep. RLS occurs more frequently in MSA-P than in MSA-C, and may be associated with iron deficiency, although studies are conflicting [45]. Physicians should review medications that may exacerbate RLS such as anticholinergics and antihistamines, and consider typical therapies such as dopaminergic agents, gabapentin (regular or enacarbil forms), pregabalin, or low-dose benzodiazepines.

History of REM behavior disorder (RBD) is a common risk factor for synucleinopathies and almost ubiquitous in MSA [4, 66]. Symptoms should be elicited in clinical history with a referral to polysomnography for objective assessment. If RBD is present, safety is foremost and includes securing the bedroom environment and sleeping partner. Patients with RBD often sleep alone, in a separate bed, or with a divider in place. Consider also padding for hard edges, a railing, or putting the mattress directly on the floor to prevent falls and injury. Despite the frequency of RBD in MSA, no specific treatment trials are available to guide pharmacotherapy and general guidelines for RBD are usually followed. First-line therapy for RBD is clonazepam 0.5 to 2 mg at night with lower doses often quite effective [119]. Given the frequency of respiratory dysfunction among MSA patients in sleep, however, clonazepam should be avoided in the context of apnea. In these situations, melatonin at a starting dose of 3 mg is an effective second-line agent, but higher doses (10–20 mg) are often needed and well-tolerated. Additional agents such as gabapentin and pregabalin have been reported as potentially effective alternatives [120].

Sleep disordered breathing such as obstructive sleep apnea is common and occurs in 37 to 65% of MSA patients. Continuous positive airway pressure (CPAP) or bilevel positive airway pressure provides benefit [121–123], but some patients experience central sleep apnea and require AutoPAP, or positive airway pressure machines that can automatically sense snoring, apneas, and hypopneas, and increase pressure until these disturbances stop. Nocturnal stridor is a particularly concerning and common symptom, with up to 13% of patients affected in one report, and is associated with oxygen desaturations, respiratory failure, and sudden death during sleep [69, 124]. In small studies, both CPAP and non-invasive positive pressure ventilation (NPPV) have shown efficacy in eliminating oxygen desaturations and stridor [121, 122], with these treatments generally well tolerated [123]. In more severe cases, tracheostomy may be considered to address vocal cord paralysis but may worsen sleep disordered breathing [125]. Because of the absence of therapeutic trials for RBD in MSA, management relies on the standard of

care for RBD with some consideration for MSA-specific medication side effects and risks. Although low-dose clonazepam is often trialed (0.5–2 mg) [126], comorbid obstructive respiratory symptom may preclude this therapy. Sustained-release melatonin is a common and likely effective alternative, with doses ranging from 3 to 15 mg nightly. Gabapentin, pregabalin, and sodium oxybate are additional second-line alternatives [120]. Although noninvasive continuous positive pressure ventilation has shown some benefit here as well, tracheostomy may be required in advanced MSA patients to prevent fatal obstruction from vocal cord paralysis [124, 127, 128].

Dysarthria, Dysphagia, and Aspiration Risk

No medical therapies have proven effective for dysarthria, dysphagia, or aspiration. Evaluation of speech and swallow by a speech–language pathologist should be considered at the initial clinical presentation and targeted therapy established as appropriate. Speech–language pathologists are an integral member of the multidisciplinary team and work closely with clinicians, patients, and their caregivers to communicate the importance of speech and swallow interventions and approaches to optimize long-term outcomes. Speech therapy can be helpful to improve both articulation and volume. Dysphagia occurs earlier in MSA than in Parkinson disease and is more severe [129, 130]. Although therapeutic swallow measures and changes in diet consistency can help, many patients aspirate (often silently) and are at risk for choking or pneumonia. Swallow difficulty, and poor appetite, can lead to failure to thrive. Percutaneous gastrostomy tube placement (PEG) and enteral feeds may be an option for patients who need supplemental nutrition, hydration, and medication delivery, but does not change disease outcome or fully protect against aspiration. Discussion of nutritional support via PEG should be done early as part of advanced directives and should involve a team approach.

Depression

Despite the frequency and severity of depression and anxiety in patients with MSA [53] with up to half of patients reporting symptoms and evidence they play a major role in quality of life, randomized controlled trials providing therapeutic guidance are lacking [50, 51]. Treatment is largely based on Parkinson disease and other parkinsonisms. Smaller studies have suggested that paroxetine may improve motor symptoms, but without affecting depressive symptoms [131]. The combination of selective serotonin reuptake inhibitors, which have a lower risk of hypotension as compared to other classes of antidepressants, with psychotherapy is a common clinical approach and recommended for MSA patients with depression or anxiety based on evidence in Parkinson disease [132].

Cognitive Impairment

Although historically thought to have limited cognitive impairment compared to other atypical syndromes and Parkinson disease, recent evidence indicates the presence of cognitive dysfunction and dementia estimated in 14 to 16% of MSA patients causing significant impact on quality of life [133]. Empiric therapy is based on data from other Parkinson disorders, and acetylcholinesterase inhibitors such as donepezil or rivastigmine are often employed with modest benefit [119].

Orthostatic Dizziness

Three of every 4 MSA patients will suffer from orthostatic dizziness and hypotension [7, 61]. The management of orthostatic hypotension begins with behavioral or lifestyle changes including increased fluid and salt intake (i.e., volume expansion), wearing compression stockings or an abdominal binder, and being mindful of exacerbating conditions such as activity in hot, humid weather. When these are not enough, pharmacological therapy is needed. Both midodrine, an α -1 adrenergic agonist, and the mineralocorticoid fludrocortisone have demonstrated efficacy for symptomatic orthostatic hypotension and are used with good effect in MSA [134–136]. Although ephedrine also functions as a sympathomimetic, evidence from placebo-controlled trials or head-to-head comparisons is lacking [137]. Droxidopa (L-threo-3,4-dihydroxyphenylserine or L-DOPS) is a synthetic amino acid precursor that is converted by dopa decarboxylase to norepinephrine, resulting in peripheral vasoconstriction [138]. The effect of droxidopa in symptomatic neurogenic orthostatic hypotension has been studied in multicenter trials involving patients with Parkinson disease and related disorders including MSA, pure autonomic failure, and nondiabetic autonomic neuropathy. An initial trial involving an open-label dose optimization phase, followed by 7-day washout, and 7-day double-blind, drug-*versus*-placebo phase demonstrated increased blood pressure and decreased orthostatic symptoms such as weakness, fatigue, dizziness, and vision disturbance with droxidopa [139]. Based on 2 subsequent multicenter trials over a 2-week treatment period, droxidopa received FDA approval for short-term treatment of neurogenic orthostatic hypotension [140–142]; however, long-term efficacy has not been shown [138, 143].

Additionally, there is emerging evidence supporting the use of atomoxetine, a norepinephrine transport inhibitor, for neurogenic orthostatic hypotension, especially in those with central autonomic failure [144–146]. Atomoxetine in one report showed comparable results (and safety) to midodrine for treatment of neurogenic orthostatic hypotension [147], suggesting potential use as an alternative agent. Amprelosetine, another norepinephrine reuptake inhibitor (NRI), developed

by Theravance Biopharma (South San Francisco, CA), is currently under investigation in a phase 3 trial for symptomatic orthostatic hypotension in subjects with MSA, PD, and pure autonomic failure (NCT03750552). CERC-301 (rislenemdaz; developed by Cerecor, Inc., Rockville, MD) is another investigational drug developed for the treatment of symptomatic orthostatic hypotension but targets the NMDA receptor 2B subunit.

Urinary Dysfunction

Urinary dysfunction is the most common autonomic symptom of MSA and is recognized as a diagnostic criterion. There are several types of dysfunction and associated medical therapies; therefore, patients benefit from care coordinated with a urologist familiar with MSA. Sphincter detrusor dyssynergy and detrusor hyperreflexia result in urge incontinence that may respond to antispasmodics, including anticholinergics [104, 116, 148]. Conservative dosing and close monitoring are important as MSA patients can easily develop urinary retention as well. Anticholinergics such as oxybutynin may also cause confusion or delirium; thus, newer agents such as solifenacin, trospium, or fesoterodine may be preferred, though definitive evidence of superiority compared to other drugs is lacking [149]. By contrast, mirabegron is an antispasmodic that stimulates β_3 -adrenoceptors resulting in detrusor muscle relaxation and decreased afferent bladder signaling, and has comparable safety and efficacy for control of urinary urgency and incontinence [150]. Hypertension is the most common side effect but comparable to anticholinergics, though antimuscarinic effects appear less common (2% vs 25%) [151, 152]. Detrusor muscle overactivity may also be addressed with botulinum injections in coordination with urology [153, 154]. In addition, excessive nocturnal polyuria (in which more than 33% of the 24-h urinary volume is secreted at night) is a common complaint among MSA patients and evidence supports the use of desmopressin (oral or intranasal spray) before bed without clear side effects in several case series [155, 156]. Finally, neurogenic urinary retention is seen in MSA and can lead to complicated or intractable urinary tract infections and impairment in kidney function. Alpha-adrenergic antagonist medications such as tamsulosin or prazosin may be helpful [58] but increase the risk of orthostatic hypotension. As a result, intermittent self-catheterization is thought to be the first-line therapy for urinary retention in MSA [157].

Erectile Dysfunction

Erectile dysfunction is a key criterion for diagnosis of probable MSA in men and, given the social stigma and patient embarrassment, is likely underreported. As a result, questions about sexual dysfunction are an essential component of the

clinical evaluation in MSA. Randomized placebo-controlled, crossover studies support efficacy in sildenafil citrate (50 mg) [6, 158]. Treatment of sildenafil should be initiated with caution, however, because of the potential for sildenafil to exacerbate orthostatic hypotension [119].

Disease-Modifying Therapies and Trials

A relatively limited number of trials to date have failed to identify an effective disease-modifying therapy. This failure likely results from an incomplete understanding of the underlying pathophysiology as well as limitations in preclinical animal models of disease and, at clinical levels of research, a lack of early and accurate assessments of diagnosis and progression of disease. Table 3 summarizes current and past efforts to develop disease-modifying therapies in MSA.

Targeting α -Synuclein

Although GCIs containing α -synuclein aggregates are associated with clinical and pathological MSA, oligodendrocytes do not produce synuclein, leaving obscure how a protein with a purported synaptic localization and function is found in oligodendrocytes. Research pursuing the possibility of oligodendrocyte expression has found little evidence to support glial expression [177–180]. Given the lack of endogenous oligodendroglial synuclein expression, the field has explored the hypothesis that there may be cell-to-cell transmission of synuclein from neurons to glia, with preclinical evidence demonstrating trans-synaptic transmission of α -synuclein between neurons, as well as transfer to glia specifically [181–186]. Clinical evidence supporting this hypothesis includes GCIs found in patients with *SNCA* triplication [187]. Synuclein expression in the brains of purportedly sporadic MSA patients, however, has failed to show increased neuronal *SNCA* gene expression [177, 179, 180]. Recent work suggests that α -synuclein can produce a variety of potentially pathogenic conformations or “strains” which may explain the variety of pathology and localization seen among α -synucleinopathies. In the case of MSA, it may be that a particular strain is predisposed to cell-to-cell transfer from neurons to oligodendrocytes [188, 189], although no such MSA-specific synuclein strain has yet been described. Impaired protein processing or degradation has also been implicated [12, 26]. In this model, either pathologic conformations of synuclein induce protein processing impairments in a feed forward mechanism or a primary impairment in autophagic or proteasomal dysfunction leads to synuclein accumulation [26, 190, 191]. Additional work has proposed not that pathologic synuclein itself is pathologic but that abnormal glial proteasomal function results in synuclein accumulation that glia bear the burden of [12, 192].

Table 3 Summary of recent and current therapeutic trials

Therapeutic drug	Target/mechanism	Phase	Outcomes	Reference
Targeting α -synuclein (inhibition α Syn aggregation and toxicity)				
EGCG (green tea extract)	Inhibition α Syn aggregation	III	No effect on progression of disease	(NCT02008721)
Lithium	Inhibition α Syn aggregation	II	Trial terminated because of severe side effects	[159]
Rifampicin	Inhibition α Syn aggregation	II	No effect on progression of disease	[160]
Sirolimus/rapamycin	mTOR inhibitor	II	Phase II ongoing	(NCT03589976)
AFFITOPE® PD01A, PD03A	Vaccines against α Syn	II	Evidence of safety, tolerability, and immunogenicity	[161]
Anle138b	Modulates α Syn oligomerization	I	Ongoing (MODAG)	[162] (NCT04208152)
NPT200-11	Small molecule inhibitor of α Syn misfolding	I	Pending phase Ib	UCB/Neuropore (NCT02606682)
PBT434 (orphan drug)	Inhibition α Syn aggregation	I	Safety, tolerability, crosses BBB (Alterity Therapeutics)	Unpublished
Anti-miR-101	Inhibition α Syn aggregation (target microRNA-101)	PreClin	Human α Syn mouse shows decreased GCIs and increased autophagy	[163]
CLR01	Inhibition α Syn aggregation, “molecular tweezer”	PreClin	Human α Syn mouse model shows decreased GCIs, synuclein oligomers, microglial activation, cell death, and motor impairment	[162, 164]
Monophosphoryl lipid A (MPLA)	TLR4 agonist, potent inducer of phagocytosis—clearance α Syn aggregates	PreClin	Human α Syn mouse shows decreased GCIs, cell death, motor impairment	[165]
Nilotinib	c-Abl tyrosine kinase inhibitor	PreClin	Phase IIa study (NILO-PD) in PD negative (NCT03205488)	[160]
VX-765 (Belnacasan)	Inhibition α Syn aggregation (CASPASE 1 inhibitor)	PreClin	Human α Syn mouse shows decreased GCIs, synuclein oligomers, microglial activation, cell death, and motor impairment	[166]
Passive immunization (PRX002, BIIB-054)	Monoclonal α Syn antibodies	PreClin	Human α Syn mouse shows decreased GCIs, synuclein oligomers, increased microglia activity	[167]
Neuroprotection				
MPO inhibitor (AZD3241, verdiperstat)	Neuroprotection	III	Phase III ongoing based on phase II improvements in PET biomarker of neuroinflammation, improved clinical scores. Given fast track designation	Biohaven 2019 (NCT03952806)
Riluzole	Neuroprotection	III	No effect on progression of disease	[168]
Mesenchymal stem cells	Neuroprotection (trophic support?)	II/III	Delayed progression of disease	[169, 170]
CoQ10	Mitochondrial function	II	Phase II ongoing	[171]
Exendin-4	Neuroprotection (GLP-1 analogue; reduces α Syn levels)	II	Human α Syn mouse shows decreased synuclein oligomers, insulin resistance, and cell death	[172]
Fluoxetine	Neuroprotection (increases GDNF/BDNF)	II	No effect on progression of disease	(NCT01146548)
[227]NMBI (Irminix)	Chelator and antioxidant	II	Phase II ongoing	NCT04184063
Rasagiline	Neuroprotection	II	No effect on progression of disease	[173]
KM-819	Neuroprotection (FAF1 inhibition)	I	Completed, well tolerated	Kainos Medicine (NCT03022799)
GDNF	Neuroprotection	PreClin	Human α Syn mouse shows decreased cell death and motor impairment	Ubhi K et al. 2010
Neuroinflammation				
Minocycline	Neuroinflammation, inhibition microglia	III	No effect on progression of disease	[174]
IVIg	Neuroinflammation	–	Pilot study showed improved clinical scores	[175]
Fingolimod (FTY720)	Neuroinflammation, reduces α Syn, increases GDNF	PreClin	Positive results in Tg mouse model MSA	[176]

The focus on synuclein has resulted in several trials targeting synuclein pathology through inhibition of

aggregation, enhancement of degradation, or immunotherapy. The European Artemis Consortium, a collaborative effort

funded by the European Union to develop treatments for MSA named after the Greek goddess of the hunt, is evaluating α -synuclein therapies in several transgenic mouse models, including an increasing number of small molecule modulators of α -synuclein.

Anle138b is a small molecule that targets and inhibits α -synuclein oligomerization and aggregation in MSA mouse models, slowing of disease progression and cell death [162]. These data have motivated a phase I trial in MSA sponsored by MODAG neuroscience solutions (http://www.modag.net/images/pressrelease_modag_series_a.pdf). An additional small molecule, *CLR01*, has been shown in preclinical studies to reduce the formation of synuclein oligomers [164]. The small molecule *PBT434* has also shown potential to reduce glial aggregates in an MSA mouse model through modulation of reactive iron species, and a phase I trial is currently ongoing for this agent as well [193, 194]. Preclinical data suggests that PBT434 mediates transmembrane reactive iron distribution, sequestering these reactive species away from intracellular proteins and thus reducing aggregation and oxidative stress. Based on this evidence, a phase I trial (U1111-1211-0052) is ongoing. The small molecule *NPT200-11* has similarly shown multiple synuclein-related benefits in animal models [195], including reduced synuclein pathology burden and astrogliosis, and improved motor function. Finally, the repurposed epilepsy drug and caspase-1 inhibitor *VX-765* has own some potential to limit synuclein aggregation, progression of motor deficits, and neuronal death in MSA animal models [196]. Along with phase II tolerability data in patients with epilepsy, further clinical trials in MSA patients are currently being pursued for VX-765.

Despite promising preclinical data and ongoing clinical trials in this area, caution is warranted given previous failed trials of drugs claiming a similar ability to affect α -synuclein aggregation. *Rifampicin* showed similar promise in MSA mouse models [197] as well in reducing β -amyloid aggregation in Alzheimer disease [198, 199]. However, a large double-blind trial in MSA patients failed to show effects on progression of disease. In addition, *polyphenol epigallocatechin-gallate (EGCG)* found in green tea showed modulation of synuclein aggregation in *in vitro* and cell models, but phase III randomized studies (NCT02008721) and (2012-000928-18) were negative.

Further preclinical evidence has implicated impairment of protein processing and autophagy in the pathogenesis of α -synuclein aggregation, spurring several clinical trials. *Lithium* was shown to enhance autophagy in *in vitro* and *in vivo* models [200–202]. A randomized, double-blind, placebo-controlled study (NCT00997672) was terminated, however, because of adverse effects [159]. Another autophagy enhancer, *sirolimus* (or rapamycin), showed similar preclinical benefits, and a clinical trial is ongoing in MSA patients

(NCT03589976). The c-Abl tyrosine kinase inhibitor *nilotinib* has also been proposed as an autophagy enhancer in α -synucleinopathies with promising evidence in animal models of Parkinsonism, but discouraging results thus far in clinical trials of PD and an unclear path forward in MSA patients. Finally, toll-like receptors and antisense oligonucleotides have been explored as possible additional therapies but remain in the preclinical phase.

Monophosphoryl lipid A (MPLA), a TLR4 selective agonist and inducer of phagocytosis, is thought to aid in the degradation of pathologic protein aggregates, reduction of GCIs, neuroprotection, and improvements in motor deficits in a mouse model of MSA [165]. In addition, TLR4 appears increased in MSA brains, suggesting it may participate in an endogenous reactive process of glial protein clearance in humans [203, 204], all of which support future testing in clinical trials.

Both passive and active (i.e., vaccines) immune therapies targeting α -synuclein with the goal of reduction or clearance are ongoing. Several studies in animal models have shown efficacy of both passive and active immunization against α -synuclein [167, 205–210]. AFFiRiS (Vienna, Austria) recently completed phase I studies (2018) on the active vaccine immunotherapies AFFITOPE® *PD01A* and *PD03A* that target α -synuclein in both MSA and PD, showing safety, tolerability, and immunogenicity. Using a passive immunotherapy approach, Prothena (South San Francisco, CA) designed a humanized monoclonal antibody against α -synuclein (*PRX002*) that in phase I studies resulted in over 96% reduction of serum α -synuclein levels and appeared safe and well-tolerated [161]. A phase 2 randomized and double-blind clinical trial, led by Roche, is now underway (NCT03100149). Similarly, Biogen (Cambridge, MA) is investigating passive immunotherapy with the antibody BIIB-054 directed against α -synuclein early PD (NCT03716570).

Antisense oligonucleotides (ASO) are increasingly being explored and used clinically to knockdown gene products in neurodegenerative diseases from Alzheimer disease to spinomuscular atrophy [211–213]. ASOs targeting the *SCNA* gene product in preclinical models of synucleinopathy have demonstrated some success [52, 214–216], suggesting they may have a role in treating MSA, although current work in this area remains in the preclinical phase. MicroRNA-101 has been found to upregulate oligodendroglial α -synuclein pathology in MSA mouse models and to be overexpressed in MSA brains [163]. *Anti-MiR-101* is currently in preclinical evaluations as a potential disease-modifying therapy.

Neuroprotective Therapies

Glutamatergic excitotoxicity is an important contributor and a well-known trigger for neuronal death. Several glutamate antagonists have been studied in CNS disorders for their

potential neuroprotective effect, in particular riluzole, currently approved for amyotrophic lateral sclerosis as a disease-modifying therapy. *Riluzole* has an indirect effect on glutamate receptors via blockade of sodium and potassium channels. Riluzole was shown to reduce behavioral deficits and striatal degeneration in a rat model of MSA-parkinsonism [217]. These promising findings spurred clinical trials of riluzole in MSA (and progressive supranuclear palsy). The NNIPPS trial compared riluzole to placebo for 3 years with survival as the primary outcome. Despite recruiting 400 patients to a trial of such a rare disease, survival was unchanged [168]. Other antiglutaminergic drugs have also been explored including estrogens, but with disappointing results [218]. *Tllsh-2910*, a specific NMDA receptor modulator, is one exception and is currently in phase III trials to evaluate efficacy for symptomatic management of ataxia in MSA (NCT03901638).

Rasagiline is a monoamine oxidase (MAO) B inhibitor with symptomatic benefit and suggested disease-modifying effect in PD [219]. The putative neuroprotective effects of rasagiline are thought to be related to mitochondrial metabolism rather than its MAOB effects [220]. A trial of rasagiline in a transgenic MSA mouse model showed evidence of decreased synuclein oligomers and improved motor function [221]. However, a subsequent phase II randomized, placebo-controlled trial in MSA patients failed to show benefit [173].

Neuroprotective strategies include also increasing levels of neurotrophic factors in the brain such as GDNF and BDNF. Both GDNF and neurturin have been explored as a potential therapeutic for PD [222, 223], but so far not in MSA. The SSRI *fluoxetine* has been shown to increase GDNF and BDNF and to rescue hippocampal neurogenesis in a transgenic mouse model of synucleinopathy [224, 225]. These preclinical findings spurred a clinical trial of fluoxetine in MSA (NCT01146548) that failed to show benefit.

Research has focused on the role of mitochondria in pathogenesis as well, with mitochondrial mutations and toxins playing a key role in striatonigral degeneration and parkinsonism in both animal models and patients [226–230]. Specific to MSA, both fibroblasts and induced pluripotent stem cells derived from MSA patients have shown a variety of mitochondrial impairments. Recent descriptions of mutations in the *COQ2* gene, which contributes to the mitochondrial electron transport protein coenzyme Q10 (*CoQ10*) biosynthesis, among possible MSA patients, have focused the field on mitochondrial pathophysiology. Clinical trial testing of CoQ10, however, has not been successful [171].

Exendin-4, an FDA-approved antidiabetic drug, is a glucagon-like peptide-1 (GLP-1) analogue that has been shown to reduce dopaminergic cell loss and monomeric α -synuclein levels in a mouse model of MSA [172]. Additional clinical evidence in PD patients [172, 231] has motivated a phase I trial in MSA.

AZD3241 is an orally bioavailable inhibitor of myeloperoxidase, a key enzyme in the production of reactive oxygen species. Treatment with AZD3241 has shown neuroprotective efficacy in the MPTP model of Parkinsonism and the proteolipid protein (PLP)- α -synuclein transgenic mouse model of MSA, delaying progression of disease [232]. As a result, inhibition with AZD3241, *verdiperstat*, is being explored in clinical trials as a potential therapy, currently in phase III (NCT02388295), sponsored by Biohaven Pharmaceuticals (New Haven, CT).

Some preclinical work has identified agents that have effects across mechanisms. For example a derivative of the FDA-approved multiple sclerosis immunosuppressive *FTY720* has shown effects both in mitochondria and GDNF expression as well as synuclein pathology in MSA mouse models [176].

Recently, *autologous mesenchymal stem cells (MSC)* treatment has been examined as a possible neuroprotective therapy, driven by the hypothesis that these cells can differentiate into a variety of supportive cell types which secrete neuroprotective and immunomodulatory agents [233, 234]. Studies in animal models provide support for this hypothesis [235, 236], and early clinical trials showed evidence for delayed disease progression but raised concern about interarterial delivery and ischemic lesions [169, 237]. A more recent trial involving intrathecal MSC administration showed that it was safe and well-tolerated, but may be associated with implantation pain at higher doses [170]. Larger controlled trials are needed to assess the safety and efficacy of MSC treatment, as well as further elucidate the mechanism.

Reducing Neuroinflammation

Increasing evidence suggests that the inflammatory response to abnormal α -synuclein accumulation and aggregation plays a key role in the pathogenesis of MSA (and other synucleinopathies). This neuroinflammatory response is mediated by activated microglia that respond to neuronal damage by secreting proinflammatory cytokines, stimulating further immune reaction, and phagocytosis of injured/diseased cells. A consequence of chronic microglial activation in neurodegenerative disorders like MSA is the perpetuation of the neuroinflammatory response and release of cytotoxic molecules that may promote further neuronal injury. Suppression of microglia-associated inflammation has thus been proposed as a potential therapeutic strategy in MSA. *Minocycline* is a tetracycline antibiotic that crosses the blood–brain barrier and has additional effects including inhibition of microglia, apoptosis, and proteolysis [238]. Despite conflicting preclinical evidence [203, 239, 240], minocycline was pursued clinically through the MEMSA trial which randomized 63 MSA-P patients to minocycline or placebo with a small subgroup receiving PET scans to assess microglial activation. Despite evidence for

decreased microglial activity, as measured by PET, after 1 year of treatment, the study failed to show clinical improvement and reported premature loss of 22 of 32 subjects in the minocycline group alone, primarily because of adverse events [174].

Although its mechanism remains poorly understood, intravenous immunoglobulins (IVIg) have been widely used in a number of immune-mediate neurological disorders. IVIg contains pooled antibodies from human plasma and is thought to reduce circulating inflammatory proteins that may mediate neurological disease. Based on this theory, IVIg was trialed in a single-center, 6-month, open-label pilot study in 7 MSA patients [175]. The study reported tolerability and improvement in clinical scores (both UMSARS I and II), but lacked controls, raising concern for potential placebo effects.

Conclusions

Treatment of MSA remains a challenge and requires a multidisciplinary approach including allied healthcare providers, rehabilitation, and supportive care. Although there are a number of effective symptomatic therapies, these treatments are limited by the multisystem nature of the disease, potential side effects, drug interactions, and relentless disease progression. These factors underscore the pressing need for disease-modifying therapies in MSA. A growing number of potentially disease-modifying agents are currently in preclinical development and include clinical trials focusing on α -synuclein modulation, neurotoxicity, neuroinflammation, trophic cell support, and even genetic modulation, among others. The success of these agents remains limited, however, by the number and validity of preclinical animal models, clinical diagnosis (especially early in disease), and the sensitivity and specificity of clinical fluid and imaging biomarkers to help with diagnosis and to monitor disease progression. In addition, an incomplete understanding of the underlying pathophysiologic mechanisms of MSA is a fundamental limitation. Specifically, the role of α -synuclein in oligodendrocyte-mediated neurodegeneration remains unclear. Despite these limitations, it is encouraging that recent research and clinical trials in MSA are increasing, raising hope for new discoveries and therapeutic developments for this devastating disease.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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