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Multiple System Atrophy Overview

Multiple System Atrophy (MSA) is a rare neurodegenerative disorder that can cause different symptoms, such as impairments to balance and difficulty with movement, poor coordination, bladder dysfunction, sleep disturbances, and poor blood pressure control. The disease was first known as Shy-Drager Syndrome. At the moment, it is believed that MSA is "sporadic," meaning that there are no established genetic or environmental factors that cause the disease. A few reports have described families with MSA, but this finding is probably very rare. Most often, the first clinical symptom a patient will note will be lightheadedness, dizziness, and episodes of passing out, but the first symptoms in some patients may include difficulty initiating movement, body stiffness, urinary incontinence, and increased falls. The autonomic nervous system is essential for controlling blood pressure, body temperature, digestion, urination, and sexual function, so MSA is largely a disease that impairs the autonomic nervous system. However, some patients don't seem to have severe autonomic symptoms, thus emphasizing the range of symptoms from person to person.

Although many clinical symptoms are also present in patients with Parkinson's disease, patients with MSA typically show symptom onset at a younger age, with the average onset in the early 50s. The journey to a diagnosis can be long and difficult. Many patients are diagnosed with Parkinson's disease first, but over time, the extent, severity, and type of symptoms change, making a diagnosis of MSA more likely.

One of the most important symptoms in MSA patients is the presence of sleeping abnormalities such as snoring and apnea, stridor, and acting out dreams. Also, subtle changes to a person's speech such as low pitch or quivering voice can also be noticed, and the clinician may notice symptoms that look slightly different from those of Parkinson's disease. The diagnosis of MSA is made clinically, and neuroimaging can sometimes assist with confirmation of a clinical suspicion.
Common and Distinguishing Features

Similarities to Parkinsonism

Both Parkinson's disease and MSA are characterized by deposits of a type of protein known as alpha-synuclein in the nervous system. Both conditions also specifically affect cells that produce dopamine, a neurotransmitter that controls motor commands. As a result, many of the same motor dysfunctions occur in the two conditions.

Unique features

Important differences distinguish the symptoms and course of MSA from Parkinson's disease and other conditions of the nervous system, such as cerebellar ataxia or pure autonomic failure (PAF). Notably, MSA affects several areas of the brain, including the cerebellum, the brain's balance and coordination centers, and the autonomic nervous system, as mentioned above.

Another distinguishing feature of MSA Is the types of cells involved. While Parkinson's disease affects the dopamine-producing neurons of a motor-controlling portion of the brain known as the nigro-striatal area, MSA affects both neurons and glial cells – the support cells that maintain the health of neurons and which outnumber neurons 10:1. Additionally, some of the glial cells affected in MSA produce myelin, the fatty substance that insulates neurons.

Mental Health Concerns

Depression, anxiety, panic attacks, and suicidal ideation may present in MSA. Some patients express inappropriate laughing or crying. Cognitive impairment, particularly seen in executive function, may occur in up to 75% of patients. Dementia is thought to be rare in MSA but may affect 12% to 18% of patients.
Types and Symptoms

MSA is broken down into two main subtypes based on the predominant symptom: MSA-predominant Parkinsonism (MSA-P), and MSA-predominant cerebellar ataxia (MSA-C). A patient diagnosed with MSA-P may over time appear to have MSA-C and vice versa, so these categorizations are not always set in stone.

**MSA-P**

MSA-P is more common than MSA-C. The most common symptoms seen with MSA-P are those that are more similar to Parkinson's disease, hence the designation. These symptoms may include slowness or difficulty moving, increased falls due to walking problems associated with shuffling of gait, resting tremor, rigidity, slurred speech, voice changes, drooling, difficulty swallowing, and lack of facial expression. The tremor usually disappears when the patient is moving and is more prominent at rest, thus the term "resting tremor."

In the early stages, this form of MSA may respond to medications used for Parkinson's disease; however, MSA-P tends to progress more rapidly than Parkinsonism. As patients pass through the initial stages, they no longer respond to Parkinson's medications. Individual variation with regard to the course of the disease varies widely. Some MSA-P patients require assistance with daily activities as early as 5 years after diagnosis and others are able to remain independent for as long as 20 years.

**MSA-C**

MSA-C patients present with symptoms that affect the cerebellum, which plays a role in synchronizing motor movement. As a result of the disease, people with MSA-C have difficulty coordinating walking, hand movements, speech, and eye movements. Sometimes they look intoxicated without having had an alcoholic beverage, so it can be useful to carry a medical card should anyone ask.

**Dysautonomia**

Dysautonomia (dysfunction of the autonomic nervous system) in MSA leads to problems regulating heart rate, blood pressure, breathing, digestion, and other internal organ functions. Patients may become dizzy or faint when they sit up or stand up – a condition known as neurogenic orthostatic hypotension (NOH). Conversely, blood pressure may be excessively high when lying down. Loss of bladder or bowel control, constipation, abnormal sweating, difficulty
with heat, sexual impotence in men, and sleep disturbances as mentioned above are also a result of dysautonomia.

**Diagnosis**

At this time, there are no specific symptoms, blood tests or imaging studies that distinguish MSA. Instead, doctors rely on a combination of symptom history, physical examination, and laboratory tests to evaluate the motor system, coordination, and autonomic function to arrive at a probable diagnosis.

Despite the diagnostic challenge MSA poses, recent research has yielded promising results in ways that may help unravel the causes and detection of this disease. Medical technology such as functional MRI (fMRI) measures activity levels in the brain and can demonstrate areas of impaired brain function.

Additionally, by applying sensitive pattern recognition techniques to certain MRI studies, medical science is increasingly differentiating the early signs of MSA from Parkinson's disease and other neurologic conditions with greater accuracy.

New studies are also finding that a particular type of lipid-transporting molecule important for production of myelin might be faulty in MSA patients and that evaluating this molecule, known as ABCA8, could provide a causative explanation and a screening tool for MSA.
Treatment

Parkinson Symptoms

Drugs used for Parkinson's disease may provide relief of muscle rigidity, slowness, and other motor symptoms for some MSA patients, though only in the earlier stages and with less effectiveness than for Parkinson's patients. Parkinson's drugs also can lower blood pressure and may worsen NOH symptoms, dizziness, and fainting episodes.

Autonomic Symptoms

To manage autonomic symptoms, patients may consider options such as increasing salt intake or taking steroid hormones or other drugs that raise blood pressure. Sleep apnea devices known as CPAP (continuous, positive airway pressure) machines can help with breathing difficulties.

Non-drug Therapies

Physical, speech, and occupational therapies offer drug-free tools for keeping muscles strong and flexible, helping prevent falls and other incidents that hasten disability. Encouraging mobility also lowers the risk of pulmonary embolism, a blood clot of an artery to the lungs, which can be fatal.

Many MSA patients succumb to secondary conditions of the disease, including pneumonia from aspirating food or saliva into the bronchial tubes. Apnea and problems with regulating blood pressure can also contribute to death. As such, these therapies are valuable as a way to closely monitor functions such as blood pressure and swallowing. Urinary tract infections due to disorders of the bladder can progress to overwhelming sepsis and lead to death.
Prognosis and Outlook

Prognosis is currently guarded, with most MSA patients passing away from the disease or its complications within 6-10 years after the onset of symptoms. Nonetheless, there is reason for hope, for, as Parkinson's research goes, so goes MSA research. Since the biology of MSA may be related to other neurodegenerative diseases like Parkinson's disease, it is possible that therapies designed for other conditions will also prove helpful for patients with MSA.

References

Differential Diagnosis

A differential diagnosis provides a sound way to evaluate the patient’s symptoms, list diseases likely to cause the symptoms, and eliminate those diseases less likely to be causing the patient’s clinical picture. Tests can help to confirm likely causes and rule out less likely diseases. Eliminating the less likely diseases helps clinicians more readily diagnose MSA.

Listed below are several conditions that should be eliminated through testing during a comprehensive differential diagnosis:

**Parkinson's Disease**

Parkinson's disease is a progressive neurodegenerative disorder that causes changes in motor and non-motor function. The key motor features are tremor, rigidity, reduced movement, and postural instability. A resting tremor is a commonly recognized feature of PD. This often starts in one side of the body, in the hands or feet. Hand tremors can appear as if the individual is rocking the hand back and forth, often referred to as a "pill rolling tremor" in allusion to the pharmacists of old who would count pills. Resting tremors can also affect the lips, chin, jaw, and legs.

Rigidity is characterized with increased resistance with passive motion. Some describe the movement as "catching and release," giving the sense of "cogwheel" rigidity.

Akinesia or bradykinesia is one of the most characteristic features of PD, as this involves difficulty in initiating movement tasks. This may present with speaking softly, decreased dexterity, reduced facial expression, and sleep disturbances. Over time, individuals might begin to feel slow in their movement, difficulty initiating and repeating actions, and stiffness of the limbs and body.

Postural instability typically presents later in the course of the disease and often causes walking disturbances known as freezing gait (feet getting stuck to the ground), a common cause of falls.
and hip fractures. The timing of when postural instability starts is used as a clinical marker of differentiating PD from non-PD disorders, like MSA. The average time from the beginning of symptoms to the first fall is much longer in PD. Among the non-motor signs, which commonly occur before the motor signs, is a decrease or absence of sense of smell. Other symptoms include forgetfulness and slowness in thinking. The diagnosis of Parkinson's disease is made clinically.

**Pure autonomic failure**

Pure autonomic failure is a diagnosis of involving the peripheral autonomic nervous system (ANS). The ANS is responsible for controlling blood pressure, sweating, urinary habits, and impotence. Symptoms associated with pure autonomic failure include a drop in blood pressure (>20 mm Hg systolic) from lying down to sitting or sitting to standing, inability to sweat, and trouble maintaining an erection in men.

**Progressive supranuclear palsy**

Progressive supranuclear palsy (PSP) is a disorder similar to PD, where patients present with problems related to movement, falls, speech changes, difficulty swallowing, changes to vision, mood, and cognitive problems. It is estimated that 3-6 in 100,000 people worldwide, or approximately 20,000 Americans, have PSP. Some of the parts of the brain that are impacted by this disease include the frontal cortex and areas that control eye movements. One of the classic signs of PSP is the inability to direct eye movement downward, leading to blurry vision when attempted.

**Dementia with Lewy Bodies**

Dementia with Lewy bodies (DLB) is the third most common cause of dementia after Alzheimer's disease and vascular dementia. This disease has symptomatic overlap with Parkinson's disease, such as rigidity, balance, and posture instability. However, dementia with Lewy bodies typically presents with more prominent cognitive problems, hallucination, and fluctuations in cognitive function. Other symptoms of DLB include dysfunction of the autonomic nervous system, REM behavior sleep disorder, and memory changes.

**Corticobasal Degeneration**

Corticobasal degeneration initially presents with motor and/or cognitive difficulties. Individuals may have problems walking, more prominent limb rigidity, and inability to perform purposeful movements, and notice problems with speech. Some patients liken the limb problems to "my arm will not obey me." Early on in the disease, the movement changes begin on one side such as the hands and legs, and later spread other limbs. Symptoms typically begin in the 60s.

**Multiple Sclerosis**
Multiple sclerosis (MS) is an immune-related disorder, where the body seems to mistake the brain for a pathogen. This disease predominately affects the spinal cord and brain. MS is more commonly found in women than men and geographically in Europe and North America. Some of the early symptoms present with a temporary loss of vision or motor movement. Diagnosis is made clinically, and with an MRI scan.

**Spinocerebellar ataxia**

Spinocerebellar ataxia is a genetic neurodegenerative disease that commonly presents in individuals 30-50 years old. The early symptoms seen are poor coordination of gait, speech, and arms. Diagnosis of spinocerebellar ataxia is predominately based on taking a thorough family history and neurological evaluation. Medical imaging and genetic testing may be used to support the diagnosis.

**References**

Evaluation Methods

MRI

Magnetic resonance imaging (MRI) is a form of imaging that is used to detect changes in the brain. Individuals with MSA may find that an MRI is useful for diagnosis, but it is not clearly needed on a yearly basis to track the disease progression. MRI can be used to differentiate between MSA-P and Parkinson's Disease, especially by looking for certain changes in the brain stem, or putamen. Due to its significant role in diagnosing MSA, MRI is considered a diagnostic tool.

PET Scan

Positron emission tomography, also known as PET, is an imaging technique that records brain activity. Physicians may use this imaging modality to better their diagnosis as certain neurologic disease impact specific parts of the brain, leading to decreased function in those areas.

Ultrasound

A transcranial ultrasound may be used by your physician to look at a part of the brain stem responsible for releasing a neurotransmitter called dopamine.

Autonomic Testing
The autonomic nervous system controls various aspects of the body such as heart rate, blood pressure, bladder, and sexual function. In Multiple System Atrophy, individuals may have an impaired autonomic nervous system, leading to dysautonomia, and are tested in a noninvasive manner. One of the possible findings includes a blood pressure drop of >20 mmHg (or >30 mmHg for certain labs) systolic from sitting to standing, known as orthostatic hypotension. There are several different ways the autonomic nervous system can be tested, but the most common is the tilt table test, where the blood pressure and heart rate will be assessed lying down, then in the raised position. Attention to the beat-to-beat variability and how the heart beat changes when the person holds their breath is another way to see the integrity of this system.

**Blood Tests**

A blood sample may help differentiate MSA from pure autonomic failure (PAF) and Parkinson's disease. Individuals with MSA have near normal levels of a neurotransmitter called norepinephrine, which is used in the autonomic nervous system. This chemical is often decreased in PAF, and is used in some centers for diagnosis of PAF (peripheral). There are no diagnostic blood tests for MSA at present.

**Clinical Exam**

Many neurodegenerative diseases are diagnosed clinically. The clinical exam should include a thorough neurological exam that consists of testing cranial nerves, reflexes, memory, coordination, movement, and speech. A neurologist may use various standardized questionnaires to improve diagnostic assessment. This is the best method for monitoring change over time of the patient.

**References**

Neurogenic Orthostatic Hypotension

Neurogenic orthostatic hypotension (NOH) is a condition in which the autonomic system, which controls the automatic functions of the body, loses the ability to properly regulate blood pressure as one moves from sitting or lying down to standing, or when one changes positions quickly. As a result, patients with NOH suffer sudden and dangerous drops in blood pressure. Doctors define NOH as a >20mm Hg drop in systolic blood pressure – the upper number of the blood pressure ratio – or a >10mm Hg decrease in the diastolic pressure – the lower number of the blood pressure ratio – within 3 minutes of standing up from sitting or lying down\(^9\). Other everyday activities that elicit an increase in blood pressure, such as digestion of food, lifting heavy objects, and defecating can also bring on an episode of NOH.

The main symptoms of NOH include dizziness and visual disturbances. Fatigue, cognitive impairment, blurry vision, and difficulty breathing also occur as part of this condition. Symptoms may occur more often or more severely early in the morning, in hot weather, after large meals, or from prolonged standing\(^1\). NOH is common in MSA, affecting about 75% of patients. (1) By comparison, up to 58% of Parkinson's disease patients and 10% to 30% of the aging population at large experience orthostatic hypotension\(^1\).

Non-Pharmacological Treatment Options
**Lifestyle Changes**

Numerous non-drug methods may help prevent or manage NOH symptoms. Patients experiencing NOH may find that lifestyle changes such as moving more slowly and carefully than they are accustomed to so as to prevent rapid changes in position, eating smaller meals, and avoiding exposure to extremes of temperature, such as going from indoor air conditioning to the outdoors on a hot day, may be in order. Rearranging activities for afternoons rather than mornings, when NOH symptoms are more pronounced, may result in fewer episodes of NOH. Heavy lifting should also be avoided.

**Compression Stockings**

Preventing blood from pooling in the legs when one stands up can keep blood pressure from falling. Compression stockings and other compression garments provide a mechanical boost to make up for the lack of autonomic control in such situations. Valuable knowledge about this method for treating NOH comes from research conducted by the aerospace industry. OH affects astronauts who have recently spent time in space, where their bodies adapt to diminished gravity by decreasing blood volume. As a result, they experience a period of OH upon their return to earth. One study showed that inflatable compression suits and specially designed compression garments increase astronauts' blood pressure and improve their ability to perform tilt tests without experiencing OH. Commercially available, custom-fit, graded compression stockings known as Jobst stockings, which have higher pressure at the ankles tapering to lower pressure around the top of the thigh, and some compression garments that include the abdomen, also perform well at preventing lightheadedness or faintness, a condition known as presyncope. These garments offer the added advantage of being non-inflatable.

**Hydration**

Drinking water, which raises blood pressure by increasing blood volume, has been found to be a particularly effective means of managing NOH. Pre-emptive water intake may increase blood pressure more than can be achieved pharmacologically. Increases of over 40mm Hg in systolic pressure have been observed within 20 minutes of rapidly drinking 480 mL or about 16 fluid ounces. Of note, plain water, as opposed to other watery fluids, seems to be a key component of this method for MSA patients. In an experiment in which clear soup was used in place of water, results were not favorable for the participants with MSA who underwent a tilt test after consuming 450 mL of clear soup. Similarly, sugary drinks have the opposite effect, lowering blood pressure instead of raising it.

**Salt and Kidney Function**

Eating a high-salt diet is an effective way to raise your blood pressure and is recommended for patients with NOH provided there is no history of kidney disease. Check with your doctor before implementing any dietary change.
NOH causes the kidneys to function differently in ways that perpetuate NOH while you are sleeping or are lying down. At such times, blood return from the lower half of the body increases, stimulating the kidneys to filter the blood at a higher rate. To offset the increased blood volume they must filter, the kidneys secrete sodium, promoting loss of water, which contributes to low blood volume, worsening NOH symptoms.

**Elevation of Head of Bed**

Raising the head of the bed by 10 to 30 degrees while sleeping can raise the standing blood pressure and help offset the low blood pressure effects of NOH. Patients may need to do this regularly for a few weeks before seeing noticeable benefits.

**Leg Crossing**

Crossing the legs can help with OH by decreasing circulation to the legs, thereby maintaining higher blood volume and blood pressure in the head. One study found that leg crossing while standing increased average arterial blood pressure in patients with either pure autonomic failure or MSA by an average of 24%, resulting in improved blood flow and oxygenation to the brain and less risk of dizziness, falling, and other complications of OH. Contracting the leg, buttocks, and abdominal muscles while using the leg crossing method can help maintain blood flow in the legs while still increasing blood supply to the head.

**Reducing Medications**

Dopamine drugs for Parkinson's symptoms and medication for high blood pressure may worsen OH symptoms and may require patients to reduce or discontinue those medications in order to effectively manage OH.

**Pharmacological Treatment Options**

Medication therapy for NOH is highly individualized. As opposed to bringing blood pressure up to normal values, which may not be realistic or necessary, the goal is to arrive at the proper drug and dosage level that most effectively manages your NOH symptoms.

**Adrenal-Supportive Drugs**

**Fludrocortisone**

One of the mainstay medicines for NOH is fludrocortisone, trade name Florinef. This drug is a synthetic adrenal corticosteroid hormone that increases blood volume and blood pressure by making the body retain sodium, thus increasing water retention. Fludrocortisone also makes cells more sensitive to adrenaline, a hormone that causes blood vessels to contract, reducing blood flow to the kidneys and slowing the production of urine. However, fludrocortisone's blood pressure-raising effects can cause blood pressure to become elevated while the patient is lying
down, a complication that can potentially lead to congestive heart failure. This and other drugs that promote adrenal hormone activity should be taken 30 to 45 minutes before activity rather than on a fixed schedule. Potential side effects of fludrocortisone include difficulty sleeping, dizziness, headache, sweating, indigestion, and nervousness\textsuperscript{17}.

**Misodrine**

Misodrine, trade names Amatine and Gutron, elevates blood pressure by making arteries and veins more sensitive to adrenaline, which causes blood vessels to contract. In a review of research studies conducted on midodrine, researchers found that it increased standing systolic blood pressure by an average of 21.5 mm Hg\textsuperscript{18}. Study participants reported significant improvement in their symptoms. Potential side effects of midodrine include difficulty initiating urination, urinary urgency, elevated blood pressure when lying down, itchy scalp, and goosebumps on the skin. Midodrine can also cause blurred vision, dizziness, fainting, headache, and pounding in the ears\textsuperscript{19}.

**Droxidopa**

Droxidopa, trade name Northera, a newer drug for managing NOH, is a chemical that the body converts to two neurotransmitters: norepinephrine and adrenaline. This versatility allows droxidopa to work within the brain, where it acts on the blood pressure-regulating center, and the body, where it influences the heart, blood vessels, and other organs to increase standing blood pressure\textsuperscript{20}.

A clinical trial that included patients with MSA and pure autonomic failure found that droxidopa improved NOH symptoms in 78\% of participants and completely eliminated symptoms in 44\% of participants\textsuperscript{21}. Drops in supine-to-standing blood pressure improved by 40\%. In another study, symptoms such as dizziness, lightheadedness, and blurred vision also improved. Additionally, droxidopa did not cause an increase in supine blood pressure. It has been in use for other indications since 1989 and has been proven highly safe with few side effects. While a small percentage of patients have experienced serious adverse events while taking droxidopa, including breathing difficulty and fainting, these instances may have been related to disease severity, as opposed to side effects caused by droxidopa\textsuperscript{22}.

**Yohimbine**

Yohimbine is an herb which stimulates production of adrenaline and activates adrenaline receptors and has been shown to prevent blood pressure from dropping upon standing from lying down by more than 10 mmHg\textsuperscript{25}. Potential side effects of yohimbine include racing or irregular heartbeat, anxiety, tremor, and confusion. Allergic reaction to yohimbine may cause swelling of the throat and difficulty breathing.

**Atomoxetine**
Atomoxetine, trade name Strattera, helps keep adrenaline in circulation. It is particularly useful if, as for most MSA patients, NOH stems from degeneration of blood pressure control centers in the brain but adrenaline receptors throughout the body remain intact\textsuperscript{23}. Potential side effects of atomoxetine include acid indigestion, cough, urinary retention, urinary incontinence, constipation, nausea, chest tightness, difficulty sleeping, and fatigue\textsuperscript{28}.

**Pyridostigmine**

Pyridostigmine, trade name Regonol, is a drug which inhibits the breakdown of acetylcholine, the main neurotransmitter of the autonomic nervous system. By doing so, it stimulates the adrenal glands to release adrenaline. Pyridostigmine produces a significant increase in standing blood pressure. It also helps avoid the problem of elevated supine blood pressure by promoting adrenaline production only during times of activity and not when one is sedentary. However, pyridostigmine has been found to be less effective in severe forms of NOH\textsuperscript{23}. In a comparison study of yohimbine with pyridostigmine in patients with MSA, Parkinson's Disease, PAF, and severe autonomic failure, yohimbine raised standing blood pressure by an average of 11 mm Hg and reduced NOH symptoms, while pyridostigmine raised blood pressure by an average of 0.6 mm Hg with no improvement in symptoms\textsuperscript{27}. Potential side effects of pyridostigmine include extreme muscle weakness and twitching, slurred speech, vision problems, severe vomiting or diarrhea, anxiety, and seizure\textsuperscript{24}.

**Rasagiline**

Rasagiline, trade name Azilect, an antidepressant sometimes used to treat Parkinson's symptoms, has been studied and found to have no effect for those with NOH and MSA\textsuperscript{34}.

**Brain Neurotransmitter Activation**

**Ergotamine**

Ergotamine, derived from the ergot fungus, resembles several neurotransmitters, including epinephrine, serotonin, and dopamine in structure. Ergotamine has been used alone or in combination with caffeine to increase blood pressure and improve NOH symptoms. However, ability of the body to absorb and utilize ergotamine varies from person to person. Also, ergotamine may not be safe for patients with heart disease\textsuperscript{23}.

**Anti-Anemia**

Patients with severe autonomic failure often develop a mild form of anemia due to impaired red blood cell production. Treating anemia with a hormone called recombinant erythropoietin can increase blood volume and blood pressure, reducing NOH symptoms. Disadvantages of recombinant erythropoietin are that it must be delivered by injection 3 times per week and is costly.
An alternative to recombinant erythropoietin is the drug desmopressin or DDAVP, a synthetic form of the blood pressure-raising hormone vasopressin. Desmopressin is injected at bedtime and is safe to use for patients with elevated supine blood pressure. However, this medication can cause low sodium levels\(^\text{23}\).

**Other Drugs and Supplements**

**Octreotide**

Octreotide, trade name Sandostatin, is a drug that mimics somatostatin, a brain hormone that controls secretion of growth hormone from the pituitary gland. Octreotide has demonstrated superior ability to raise blood pressure by constricting veins and offers similar effectiveness to midodrine for improving prolonged standing ability. Octreotide can be used in conjunction with midodrine; however, it must be injected. Potential side effects of octreotide include abdominal pain, blurred vision, constipation, depression, dizziness, fainting, increased urination, fatigue, and difficulty breathing.

A review of previous studies found that the drugs indomethacin, a nonsteroidal anti-inflammatory agent, and the supplement potassium chloride raise blood pressure, on average more than 10 mm Hg\(^\text{25}\). Potential side effects of indomethacin may include acid indigestion, nausea, vomiting, and diarrhea. Potassium chloride side effects may include nausea, vomiting, and diarrhea as well\(^\text{32}\).

Patients have also reported improvement in symptoms with a combination of the herbs camphor and hawthorn berry\(^\text{25}\). The herbal combination has been tested in clinical trials and found effective for some patients with NOH. These substances are generally considered safe and well-tolerated\(^\text{31}\), though some patients experience fatigue, nausea, or sweating from taking hawthorn berry\(^\text{33}\).

**References**

2. [http://medicine.ucsf.edu/education/resed/Chiefs_cover_sheets/orthostatic.pdf](http://medicine.ucsf.edu/education/resed/Chiefs_cover_sheets/orthostatic.pdf)
Neurogenic Bladder

The ability to store urine for several hours at a time and release it at convenient intervals relies on a complex coordination of nervous system feedback loops to and from the bladder, spinal cord, and brain. Many junctures along these feedback loops are vulnerable to the effects of injury or illness. As such, urinary dysfunction is a common feature of neurologic conditions. In MSA, urinary problems usually arise from degeneration in a part of the brainstem that controls urination. Symptoms such as incontinence, leakage, urinary frequency and urgency affect up to
96% of MSA patients and are often one of the first signs to appear. Urinary problems that go untreated can lead to infections, kidney damage, and kidney stones. Chronic urine leakage that is poorly managed can also cause skin damage and pressure sores around the genital area. Accurate diagnosis and prompt treatment can help prevent urinary problems from progressing.

One of the ways bladder control malfunctions is by failing to allow complete emptying of the bladder. Patients may be unaware that their bladder is not emptying fully and only suspect a problem when they find themselves having to void again within minutes. An ultrasound study can determine whether the bladder is retaining urine and how much is being retained.

Another problem associated with inability to void urine is lack of control of the urinary sphincter, the circular muscle at the opening of the bladder that contracts to retain urine and relaxes to allow emptying of the bladder. This lack of control is a prevalent condition in MSA patients, affecting up to 77% of patients who have urinary symptoms. Similarly, the muscle in the wall of the bladder, called the detrusor muscle, which normally contracts to expel urine from the bladder, can become overactive. In MSA, detrusor overactivity results in sudden urgency and leakage of urine, a condition known as urge incontinence.

The pattern of urinary symptoms forms an important distinguishing feature that helps doctors differentiate between MSA and Parkinson's disease. In PD, 58% of patients experience urinary problems, whereas urinary symptoms affect the overwhelming majority of MSA patients. The majority of affected Parkinson's patients have difficulty with the storage of urine more so than voiding, and symptoms appear later in PD than they do in MSA – usually 5 or more years after diagnosis, compared to less than 2 years post-diagnosis in MSA patients. MSA patients generally experience problems with both urine storage and voiding.

Non-Pharmacological Treatment Options

Intermittent Self-Catheterization

If ultrasound evaluation reveals that there is residual volume of 100 mL, or more than one-third of your bladder capacity, your doctor may recommend intermittent self-catheterization. For this procedure, the patient or a caregiver will insert a flexible plastic tube, called a catheter, into the urethra and up into the bladder to allow residual urine to drain. A regular schedule of catheterization immediately upon awakening in the morning, every 3 to 4 hours throughout the day and evening, and just before retiring for the night. It is important to perform catheterizations at regular intervals to prevent infection that may occur due to residual urine being present in the bladder for prolonged periods of time.

A urologist's training staff will demonstrate sterile technique for self-catheterization and the patient will be asked to show proficiency with the method. A red rubber catheter, a sterile wipe, gloves, and lubricant jelly are all that is needed. Be aware that there are self-lubricating, individually packaged commercial products available for use when away from the home. Multiple types of catheter units are available. Find the one that the patient is most comfortable using. These are more convenient than nonlubricated catheters, but they tend to be more
expensive and insurance may not cover the cost.

**Permanent (Foley) Catheter**

Patients might require a permanent, indwelling catheter, known as a Foley catheter, if intermittent self-catheterization becomes ineffective or inconvenient. Foley catheters have a balloon at the end that is inserted into the bladder. When the catheter is properly positioned, the balloon is filled with sterile water to keep the catheter in place. The part of the catheter tube that passes along the inside of the thigh is then taped to the thigh to prevent the catheter from shifting.

Maintenance of a Foley catheter requires careful attention to hygiene and optimal catheter function. It is important to visually check the collection bag to make sure there is no blockage and that the urine remains clear. The urine may contain sediment after prolonged catheterization. Patients will need to wash the area of the catheter so that it remains clean. The catheter may be changed at intervals recommended by a doctor. This procedure can be performed at home or at the doctor's office by a nurse or trained caregiver. The doctor may order a full urinary work-up, which may include an ultrasound and periodic X-rays to monitor bladder health while using a Foley catheter.

**Bladder Diary**

To help ensure that the self-catheterization program is successful, patients will likely be advised to keep accurate records of fluid intake, voiding schedule, and amount of urine collected. It is recommended to consume about 1.8 L (61 fluid ounces) of fluid and to void approximately 1.6 L (54 fluid ounces) of urine per day. Patients can accomplish these goals by drinking 400 mL with each meal and an additional 200 mL at 10 a.m., 2 p.m., and 4 p.m. To avoid the need for catheterization during the night, restrict fluid consumption after dinner to sips. This may pose a dilemma. Patients must make sure to stay adequately hydrated so as to avoid NOH, so be cautious. If it is necessary to get up during the night to cath, hydrate with a sip of water before moving to an upright position. Otherwise, you are at risk for a syncopal or fainting episode.

**Bladder Retraining**

In some instances, an overactive bladder wall muscle can be retrained by carefully timing catheterization intervals. If you doctor recommends trying this technique, after taking initial recordings of time and urine volume collected, you will gradually lengthen the intervals between catheterization so that your bladder holds more urine with fewer inappropriate contractions of the bladder wall. A physical therapist trained in urodynamics can help with bladder retraining and pelvic strengthening. Patients might start by setting the interval time for 15 minutes longer than the previously established interval time. If the urge to urinate occurs before the extra 15 minutes is up, attempt to distract yourself by contacting the pelvic floor muscles. These contractions, known as Kegel exercises, stop the flow of urine and also inhibit the detrusor muscle. Start by contracting these muscles for 3 to 5 seconds. Gradually build up to 10-second contractions. Crossing of the legs and focusing on taking slow, regular breaths can also help patients reach the
goal interval time.

**Surgical Options**

If intermittent self-catheterization becomes problematic or ineffective, doctors may recommend a permanent form of catheterization known as a suprapubic catheter. In this procedure, a catheter is inserted into the bladder through an incision made just above the pubic bone. The bladder will drain through the catheter into a collection bag. The patient or a caregiver will need to replace this catheter at home every 4 to 6 weeks. Particular attention to proper care of the skin around the catheter is important in order to prevent infection. Patients will need to clean and bandage the catheter site daily and monitor for signs of infection, such as redness, pain, or swelling. The collection bag should be placed below the incision level so that gravity prevents urine from backing up into the bladder and should be situated so that the tube does not become kinked.

**Pharmacological Treatment Options**

**Propiverine**

A member of the anticholinergic family of drugs, propiverine works by blocking the activity of the neurotransmitter acetylcholine, which signals muscles to contract. In neurogenic bladder patients, propiverine decreases overactivity of the detrusor muscle, thereby increasing bladder capacity. In men with neurogenic bladder who also have benign enlarged prostates, propiverine combined with certain prostate medications has proven effective for improving urine storage capacity.

**Oxybutynin**

An anticholinergic drug, oxybutynin, brand name Ditropan, decreases an overactive detrusor muscle and can be used in conjunction with an indwelling or permanent urethral catheter. Oxybutynin helps prevent bladder leakage and backup of urine into the kidneys. It is available in immediate-release tablet form, which is more cost-effective but is associated with more side effects than other anticholinergic drugs, or in extended-release form. Patients can also take oxybutynin as a transdermal patch, from which the drug is absorbed through the skin. The patch form of oxybutynin causes fewer side effects than the oral form.

Other anticholinergic drugs used for neurogenic bladder include:

- **Tolterodine** (Detrol), a drug that is highly specific to the bladder, giving it a lower overall side effect profile than other anticholinergic drugs.

- **Solifenacin** (Vesicare), an increasingly popular newer-generation anticholinergic for use in women and also particularly effective in elderly patients and those with cognitive dysfunction.

- **Darifenacin** (Enablex), a drug that is safe for patients with heart problems or cognitive impairment.
The most common side effect associated with anticholinergic drugs – and one of the major reasons patients discontinue taking these drugs – is dry mouth. In general, extended-release forms of these drugs are associated with lower incidence of dry mouth due to lower peak blood levels compared to the immediate-release forms. A comparison study between properivine and oxybutynin found that properivine was less likely to cause dry mouth. Other anticholinergic side effects include urinary retention (affecting men more than women), dry eyes, and constipation.

**Nitric Oxide**

This chemical messenger, mostly known for its role in blood vessel dilation, also controls nerve pathways of the urinary tract. An animal study reported that raising levels of nitric oxide increases bladder capacity and improves the ruination reflex in spinal nerve injury. In another study, nitric oxide was found to relax the muscle of the bladder neck.

- Certain drugs used for erectile dysfunction are thought to work by influencing nitric oxide levels in the prostate. These drugs, known as phosphodiesterase type 5 (PDE-5) inhibitors, include sildenafil (trade name Viagra), tadalafil (trade name Cialis), and vardenafil (trade name Levitra). They are useful for improving both urinary and erectile dysfunction in men with benign prostatic enlargement.

- Vardenafil might improve sensory nerve transmission from the bladder to the spinal cord and brain and inhibit the bladder from contracting at times other than during urination.

- Tadalafil in combination with tamsulosin (trade name Flomax) – a drug used to treat benign prostatic hypertrophy or enlargement of the prostate – demonstrated a synergistic effect that relaxed the prostate and the bladder neck to a greater degree than either drug alone in a preliminary study. Tamsulosin has been shown to help alleviate urge incontinence, decrease residual urine in the bladder, decrease overactive detrusor muscle, and increase speed of urine flow and bladder storage capacity in neurodegenerative bladder dysfunction.

- A clinical trial of tamsulosin found that it increased urine flow rate by an average of 45% and decreased residual urine volume by 30% in patients with intact detrusor muscle function. However, the drug was not as effective in patients with detrusor muscle atrophy. Potential side effects of tamsulosin include cough, fever or chills, lower back pain, or difficult or painful urination. Tamsulosin may also cause chest pain, dizziness, fainting, and prolonged or painful erections.

Potential side effects of PDE-5 inhibitors include headache, flushing, stomach upset, and nasal congestion. There have also been occurrences of sudden, irreversible hearing loss following use of these drugs.
**Baclofen**

This GABA-promoting drug has been found to help calm overactive bladder, improve urinary sphincter function, and increase bladder capacity\(^7\). Baclofen (trade name Lioresal) can be taken in pill form or as an injection into the space around the spinal cord via a pump, a delivery method known as intrathecal injection. A small clinical trial found that baclofen significantly slowed progression of urinary symptoms\(^20\). Potential side effects include allergic reactions, such as skin rash or swelling of the lips or tongue, chest pain, hallucinations, and seizure. Patients may also experience sleeping problems, headache, or nausea.

**Botulinum Toxin**

If medication proves ineffective, your doctor may recommend an injection of botulinum toxin (trade name Botox) into the bladder wall as an alternative. This therapy calms an overactive detrusor muscle and increases bladder capacity\(^21\). Potential side effects include urinary tract infection and retention of urine, though it is considered safe and is associated with a low rate of occurrence of side effects\(^9\). Botulinum toxin may also be recommended in patients unable to perform self-catheterization. The injections temporarily paralyze the external sphincter and help with bladder emptying. Each injection lasts 3 to 9 months. This simple procedure is less invasive than surgery and there are minimal side effects associated with it\(^7\).

Reference 24 offers a good summary of the neurogenic bladder topic.

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MSA-P (Parkinsonian)

MSA-P is the Parkinsonian form of multiple system atrophy. It is the most common form of MSA with signs and symptoms similar to those of Parkinson's disease.

- Rigid muscles
- Difficulty bending your arms and legs
- Slow movement (bradykinesia)
- Problems with balance and posture

It should be noted that MSA patients can have a mix of MSA-P, MSA-C and dysautonomia. Depending on the mix symptoms and their severity can vary.

Non-Pharmacological Treatment Options

Physical Therapy and Exercise

Physical therapy can significantly improve motor symptoms through one-on-one exercises and personalized exercise plans. Many of the activities used to enhance movement of individuals with Parkinson's disease are used for people with MSA. The goal of physical therapy is to maintain mobility through strengthening exercises. Assisted treadmill exercises where part of the person's weight is supported lead to better balance, stability, and gait. If a treadmill is unavailable, other walking activities can be performed in a pool. Alternative forms of exercise such as yoga, tai chi, and Pilates can improve strength, flexibility, and coordination. The key to maintaining good daily function is continued activity through exercise.

Occupational Therapy

Occupational therapy has been shown to have a positive impact on individuals with MSA. An occupational therapist aims to make day-to-day living and activities easier by improving symptoms management, use of home equipment to improve mobility, and home adaptations. Occupational therapy may benefit individuals that have difficulty dressing, eating, using the computer, and other daily activities. An occupational therapist can visit the home to identify fall risks and offer recommendations to improve patient safety at home.

Speech Therapy

A speech therapist can help provide a holistic approach to taking care of individuals with MSA-P with speech difficulties. Difficulty swallowing is a frequent complaint of individuals with MSA-P and is noted to develop early in the disease. Some of the speech difficulties may include talking with a softer tone, changes in pitch, or difficulty pronouncing words. A speech therapist
may recommend a series of oral motor exercises, breathing techniques, communication support groups, and vocal exercises to improve speech.

**Pharmacological treatment**

**Levodopa**

Levodopa, also known as Sinemet, is a medication that helps increase dopamine in the brain to treat Parkinson's disease. A potential side effect seen with levodopa is an abnormal increase in body movement, called dyskinesia. The success of this medication for MSA-P individuals varies for each patient and can diminish over time. Consequently, symptoms may return between doses, and an initial effect may lessen. Typically, levodopa has been seen to be useful for MSA-P individuals for about 2 to 3 years. Therefore, to maximize its therapeutic effect and minimize side effects, patients should have a levodopa trial as soon as possible.

**Dopamine Agonists**

Dopamine agonists work very similarly to levodopa as they try to mimic dopamine but are less effective. However, some of the side effects of this class of medication include increased sleepiness, dizziness, fainting, uncontrolled movements, or behavioral changes known as impulse control disorder. Pramipexole, trade name Mirapex, has been used with success in MSA patients who do not respond to levodopa. In one study, pramipexole improved speech, swallowing, and activities of daily living such as the ability to dress or to use eating utensils. Potential side effects of pramipexole include daytime sleepiness, dizziness, fainting, nausea, difficulty sleeping, and uncontrolled movements. Another dopamine agonist includes apomorphine, trade name Apokyn, that can help treat muscle stiffness and loss of muscle control. This medication can cause a drop in blood pressure.

**Amantadine**

This antiviral medication can be used to treat mild symptoms of Parkinson's disease. This medication is thought to act on receptors on the muscle to reduce tremor and other movement disorder symptoms. Some of the potential side effects include blurred vision, confusion, and urinary retention.

**Antidepressants**

Certain antidepressants work by increasing the levels of serotonin, a neurotransmitter used in mood and movement, in the brain to improve speech, facial expression, and depression. Side effects from this medication may include irregular heart rhythm, dizziness, nausea, restless legs, and sexual dysfunction.
MSA-C (Cerebellar Ataxia)

Cerebellar ataxia is characterized by a lack of control of postural muscles combined with decreased coordination of the arms and legs resulting in a wobbly, wide-based, staggering gait. Distinct from the shuffling gait of Parkinsonism, the wide stance of cerebellar ataxia helps patients feel more stable and prevents falls and injuries. If you are affected by this condition you may also experience imprecise control of your arms and hands when you reach for, grasp and manipulate objects with your hands. Muscles that control speech can also be affected in this condition, leading to slurred, drunken-sounding speech. Additionally, tremors can occur, particularly of the head and upper trunk, but also in the arms, legs and lower trunk, depending upon which parts of the cerebellum are affected.

Nonpharmacological treatment

Physical Therapy

Physical therapy works to improve an individual's balance and gait so that the patient can try to be as independent as possible. The goal of physical therapy is to help promote the patient's awareness of his/her own body which will help with coordination and tasks. Physical therapy can work to maintain and strengthen the legs, back, and abdomen to improve walking. Also, therapists may show patients exercises to practice their eye and muscle coordination. Other activities that may be beneficial are yoga, tai chi, and Alexander technique, a form of relaxation and therapy that may be provided by some physical therapists, to continue being active and to practice mindful movement.

Occupational Therapy

Occupational therapists work to improve the daily activities of individuals to improve their mobility and can help identify possible falling risks at home. For instance, video games can improve hand-eye coordination, which may be beneficial to dexterity in patients.

Acetyl-DL-leucine

A publication described the benefits of amino acid acetyl-DL-leucine in some types of degenerative cerebellar ataxia. This study showed that 5 grams of actyl-DL-leucine per day for a week decreased ataxia rating scores by 20%. Also, there were improvements in gait, speech, and motor coordination.1
Speech Therapy

As in MSA-P, speech therapy can be useful in dealing with similar symptoms seen in MSA-C.

Pharmacological treatment

Overall, there are no therapies that modify disease progression in MSA, PD, or other related disorders. There are some that will be used in an attempt to improve symptoms, but these are used on an individual basis.

Gabapentin

Gabapentin, also known as Neurotonin, is a medication that modulates gamma-aminobutyric acid (GABA) levels in the brain. Gabapentin has a relatively safe medication profile with few side effects. These side effects would be fatigue, sleepiness, dizziness, rolling eye movements, and weight gain. It can help with pain, stiffness, sleep problems, and to stabilize mood.

Pregabalin

Also known as Lyrica, pregabalin works very similarly to gabapentin by modifying GABA concentrations in the brain. This medication is considered to be stronger than gabapentin. Side effects may include double vision, tremor, and impaired cognition.

Baclofen

As in MSA-P this medication works by modifying GABA in the brain and can improve spasticity. Side effects of this medication include impaired cognition, irregular heartbeats, drowsiness, fatigue, and changes to bladder function.

References

Dystonia

Dystonia is a neurological condition that causes muscles to contract involuntarily and out of proper sequence. It can occur anywhere in the body, including the muscles of the arms, legs, trunk, or face, and appears as repetitive, twisting movements and unnatural posture. About 50% of MSA patients experience dystonia.

Not an early symptom of MSA, dystonia tends to manifest as the disease progresses and occur more commonly in MSA-P than MSA-C. Though botulinum toxin injection is the first-order treatment for dystonia, non-drug treatment options, such as physical and occupational therapy, often improve results when combined with botulinum treatment. In some instances, neurosurgery may also be an option.

Common Forms of Dystonia in MSA

Dystonia of the cervical spine is common in MSA patients, though some experts contend that it is not an actual dystonia, but a form of Parkinsonian-type muscle rigidity. Also referred to as torticollis, it causes a severe forward or backward bending of the head. Because it affects the orientation of the head in space, cervical dystonia can contribute to balance and gait problems. MSA patients also often experience dystonia of the muscles of the mouth and face that alters speech, resulting in high-pitched sounds. Dystonia of the vocal cords can occur and contribute to obstructive sleep apnea. Dystonia of the trunk muscles alters posture and gait in some MSA patients.

Non-Pharmacological Treatment Options

Physical and Occupational Therapy

Physical and occupational therapists can help in the management of dystonia by mobilizing joints to maintain range of motion and stretching muscles to minimize contracture, or permanent shortening of the muscle. Targeted sensory stimulation via certain orthopedic devices can help inhibit overactive muscles and activate weak muscles to achieve more balanced muscle function around a joint or body part. A form of movement-retraining therapy called constraint-induced therapy is used in dystonia of the hands. This approach involves
taping or splinting non-dystonic fingers as a way to isolate the dystonic fingers and encourage them to function.

Physical therapy for dystonia of the neck may include a form of motor retraining in which the patient repeatedly moves his or her neck in the opposite direction to the dystonic movement. Passive and active stretching techniques help mobilize the cervical spine. Additionally, low-level electrical stimulation on the skin surface can activate the non-dystonic muscles. This causes a reflex that inhibits and relaxes the overactive, dystonic muscles. In a study that compared physical therapy combined with botulinum treatment to botulinum treatment alone, severity of dystonia decreased in both groups, but only the group that received the combination of treatments experienced a decrease in pain levels. Additionally, mental health, vitality, and sociability improved in the group that received physical therapy but not in the botulinum-only group.

For dystonia of the trunk muscles, one case-report study used botulinum toxin injections along with a combination of active and resisted movement exercises, stretching, athletic taping, functional rehabilitation, and sensory maneuvers. The results included improved posture and function, decreased pain, and lower doses of botulinum toxin needed.

While a mild stooped posture is a common characteristic of Parkinsonian conditions, some MSA patients with trunk muscle dystonia develop an extremely forward-bent posture known as camptocormia. Standing and walking worsens camptocormia symptoms, but when some patients with camptocormia lie down, the back straightens. Though its cause is not fully understood, it is thought to be either a form of trunk-muscle dystonia, unbalanced muscle rigidity, or a muscular disease. A type of orthotic device comprised of two braces, one around the lower ribcage and one around the pelvis, connected by a rigid spacing bar has been found helpful in patients with camptocormia that resolves in the lying-down position.

**Sensory Tricks**

Touching a part of the face or head can help some patients reorient their posture. The technique, known as geste antagonistique, was found, in one study, to be effective for correcting head position in half or more of patients. Simply thinking of the sensory cue is effective for some patients. Also, wearing a device that creates continuous contact with geste antagonistique points has been found helpful.

**Biofeedback**

Electrode sensors placed over involved muscles can give the dystonia patient a continuous stream of cues, or feedback, about the activity of those muscles. In a typical biofeedback session, information from the electric sensors is projected onto a computer screen and the patient is prompted to alter his or her position or movements in accordance with the information on the screen. Biofeedback has been found to offer similar benefits to some forms of physical therapy.
Surgery

In severe cases of dystonia, surgery may be considered. Surgery for dystonia involves severing the peripheral nerve or nerves that supply the affected muscles. For cervical dystonia, this procedure works well on a limited number of patients with specific patterns of dystonia, particularly those that are purely rotational\(^3\). Adverse effects of the surgery tend to be temporary, but can include balance problems and swallowing difficulties\(^3\).

Pharmacological Treatment Options

Botulinum Toxin

Injections of botulinum toxin, trade name Botox, particularly in the deeper muscles of the neck, have been found helpful for cervical dystonia\(^5\). Botulinum has also been used successfully and with significant pain reduction in dystonias of the mouth, jaw, and tongue, as well as in dystonias of the trunk muscles\(^5\). However, dystonias of the legs may not respond as well to botulinum therapy as cervical and arm dystonias\(^13\). A review of previously published studies found that botulinum toxin offers significant improvement, particularly for tremor associated with dystonia, compared to drug therapies, including anticholinergic drugs, levodopa, clonazepam, beta blockers, and primidone, which offer limited benefits for dystonia\(^15\). Side effects of botulinum toxin therapy, including dry mouth and swallowing difficulties, occur in up to 19% of patients\(^14\).

Levodopa

The compound levodopa, sold commonly under the trade name Sinemet, may be helpful for alleviating dystonia in a minority of MSA patients. In one case-report study, researchers noted that camptocormia, a dystonia characterized by an extremely forward-flexed posture that occurs when standing but goes away when the patient lies down, was alleviated with levodopa in an MSA-P patient\(^16\). Side effects of levodopa can include nausea, movement disorders, sleepiness, orthostatic hypotension, and cognitive impairments\(^17\).

Anticholinergics

A category of drugs known as anticholinergics is often used to treat dystonia. These drugs work by blocking acetylcholine, the neurotransmitter that activates muscles. Examples include benztrapine (Cogentin), biperiden (Akineton), procyclidine, and scopolamine (Scopace or Maldemar)\(^17\). However, because anti-cholinergic drugs need to be taken in high doses, side
effects are common and may include sleepiness, cognitive impairment, constipation, urinary retention, insomnia, blurred vision and dry mouth”.

**Tetrabenazine**

This drug, sold as which lowers dopamine levels, is primarily used to treat Huntington's disease and has also shown some effectiveness for dystonia”. Side effects of tetrabenazine, trade name Xenazine, include sleepiness, parkinsonism, cognitive impairment, depression, orthostatic hypotension, and insomnia”. Tetrabenazine has demonstrated effectiveness in treating cervical dystonia in Parkinson's patients”.

**Baclofen**

This drug, trade name Lioresal, raises levels of the calming neurotransmitter GABA and is helpful for some dystonia patients”. Side effects may include sleepiness, nausea, cognitive impairment, dizziness, and muscle weakness. Baclofen use causes dependency, and stopping or suddenly lowering the dose can result in seizures and delirium”.

**Benzodiazepines**

This category of drugs, including clonazepam (Klonopin), diazepam (Valium), and lorazepam (Ativan), increase GABA activity and may be helpful for some forms of dystonia. However, these drugs can cause dependence, resulting in seizures and delirium if they are suddenly stopped or if the dose is lowered too quickly”.

**Zolpidem**

A GABA-enhancing drug called zolpidem, trade name Ambien, primarily used for insomnia, has also been shown to improve dystonia symptoms”. In one study, 37% of participants responded well to zolpidem”. In the same study, 25% experienced improvement with clonazepam and 19% improved with baclofen. Zolpidem has been found to be helpful for hand and face dystonias but less helpful for cervical dystonia. The most common side effect of this drug is drowsiness”. Other potential side effects of zolpidem include headache, muscle aches, stuffy or runny nose, constipation or diarrhea, indigestion, double vision, and movement difficulties”.

**Muscle Relaxants**

This broad range of drugs that includes some already mentioned, such as baclofen and benzodiazepines, as well as others, including carisoprodol (Soma), cyclobenzaprine (Flexeril), metaxalone (Skelaxin), and methocarbamol (Robaxin), can be helpful for managing pain of pulled or sore muscles that can occur often in dystonia”. Side effects of muscle relaxants are common and include drowsiness, dizziness, urinary retention, and dry mouth. These drugs also can be addictive”.

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www.multiplesystematrophy.org
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Breathing Disorders

Disorders affecting breathing are common in patients with MSA and may arise from atrophy or overactivation of breathing or vocal cord muscles or a combination of the two\(^1\), as well as degeneration in areas of the brain that control respiration\(^2\).

In one type of breathing disorder, known as stridor, a characteristic wheezing sound occurs when inhaling. Stridor, which occurs in up to 42% of MSA patients\(^6\), results from overactive vocal cord muscles that remain constricted, closing down the airway, when they should relax, such as during inhalation. In some patients, overcontraction of muscles that constrict the throat occurs along with atrophy, or underactivity of muscles that expand the throat\(^4\). Stridor can occur throughout the day and night, or, in some instances, only during sleep\(^3\). Patients affected by stridor may experience increased respiratory rate and heart rate during sleep\(^7\).

Stridor during sleep also can cause obstructive sleep apnea, a condition characterized by frequent, prolonged periods when breathing stops. Obstructive sleep apnea affects about 37% percent of MSA patients\(^6\) and episodes have been documented to occur as often as 32 times per hour\(^4\). Sleep apnea disrupts the phases of sleep, causing arousal from deep sleep and leading to poor sleep quality and associated physiological stress, such as lowered immune function and daytime fatigue. Decreased blood oxygen levels also result from sleep apnea, with one study reporting oxygen saturation dropping to as low as 86%, compared to a normal, healthy level of 95% to 100%\(^5\). Waveforms of stridor in MSA can be either rhythmic or semirhythmic in pattern. The authors of this review concluded that in MSA, stridor composed of the rhythmic component has a poorer outcome\(^38\).

Non-Pharmacological Treatment Options

CPAP
For sleep apnea or nocturnal stridor, a doctor may recommend using a continuous positive air pressure (CPAP) machine. This device applies air pressure into the airways to keep them open. A pump creates the pressure, which is delivered through a hose connected to a face mask worn while sleeping. At first, some patients experience claustrophobic feelings from wearing the mask. As a result, it might take a few nights of using the CPAP to become accustomed to it. Pressure from the mask, which must be worn snugly to maintain the correct amount of air pressure, can also cause nasal congestion, sore or dry eyes, headache, or a skin rash where the mask contacts the face. Some simple remedies can help manage irritations caused by the CPAP. "Artificial tears" eye drops can alleviate dry eyes, nasal salt sprays and room dehumidifiers help reduce nasal stuffiness, and skin moisturizer or protectant patches help prevent skin sores where the mask contacts the face.

Use of CPAP machines has been found to improve quality of sleep and increase alertness during the day in some MSA patients. Patients who start CPAP therapy as early as possible after breathing problems arise tend to have better results and stay with the therapy over a longer-term. Studies have shown that CPAP use can eliminate or reduce stridor and obstructive sleep apnea and improve blood oxygen levels.

**BiPAP**

A form of positive airway pressure therapy known as bi-level positive air pressure, or BiPAP, also called adaptive servo-ventilation, assists breathing by not only using pressure to open the airways, but also by increasing the depth of respiration. A BiPAP machine is capable of modulating air flow to maintain the correct pressure to counteract the effect of air leaks in the mask or variations in the patient's breathing rate and depth. BiPAP may be useful in some patients with sleep apnea who have degeneration of sleep centers in the brain, known as central sleep apnea, in addition to or instead of airway obstruction. In one study of MSA patients with central sleep apnea, BiPAP use eliminated stridor and improved blood oxygen levels.

**Tracheostomy**

If sleep apnea is particularly severe or if stridor occurs during waking hours as well as at night, a CPAP machine may be impractical or ineffective. Instead, the doctor may recommend a surgical procedure called a tracheostomy. In this procedure, an opening is made in the trachea (windpipe) through the neck, and a tube is connected from the trachea to the outside so that air can more easily enter and exit the lungs. Some tracheostomy tubes are fitted with an inflatable cuff to provide a better seal between the tube and the opening in the neck. This prevents air or unwanted substances such as water or smoke from seeping in around the tube and increases air pressure between the lungs and the external environment, promoting better airflow and improving breathing.

Learning to breathe through a tracheostomy tube may take a few days of practice. Speaking with a tracheostomy tube also is challenging at first, and may require special
training. A tracheostomy requires proper cleaning and care, including regular suctioning to remove secretions from the lungs. Adverse events that might occur soon after tracheostomy surgery include bleeding around the opening, infection, obstruction of the tube, air entering the chest cavity (pneumothorax), and nerve damage. A tracheostomy that remains in place permanently can cause long-term complications such as difficulty swallowing, blood vessel rupture, and formation of scar tissue. Impaired blood supply to the trachea and formation of a fistula, or abnormal connection between trachea and esophagus (food pipe), are other risks associated with tracheostomy.

Other Surgical Options

Certain structures in the throat aside from vocal cord muscles can contribute to obstructive sleep apnea. Surgical options depend on which structures might be contributing to the problem. If tonsils are enlarged, a tonsillectomy may be in order. In another surgery, part of the soft palate and the uvula, the fold of tissue that projects down from the soft palate, are removed to create more space in the throat. The procedure, known as uvulopalatopharyngoplasty (also called UPPP or UP3), was shown in one study, to decrease episodes of disordered breathing by more than half in 60% of patients with obstructive sleep apnea. However, the study also found that the majority of patients who have the surgery develop long-term side effects, including impaired ability to fully close the soft palate, a problem that can interfere with certain speech sounds.

A Cautionary Note

Though a rare occurrence, vocal cord muscles can become completely paralyzed, totally obstructing air flow. This constitutes a medical emergency and can happen regardless of which form of therapy the patient undergoes. In one instance, a MSA patient developed complete upper airway obstruction upon being anesthetized in preparation for microlaryngoscopy, an imaging procedure that involves passing a tube with a video camera into the throat. To avoid respiratory failure when breathing problems arise due to vocal cord paralysis, exercise vigilance and be prepared to respond rapidly.

Pharmacologic Treatment Options

Botulinum Toxin

Injections of botulinum toxin can help relieve constriction of the larynx if sleep apnea is caused or worsened by dystonia of the throat muscles. Botulinum injections may cause speaking and swallowing difficulties in the initial phases following injections. In one study, 51% of treatments resulted in moderate voice impairment and 14% of treatments caused participants to experience difficulty swallowing liquids. These side effects lasted for 5.7% of the total time between treatments and resolved as the effects of the toxin wore off. Overall, botulinum therapy produced a 30% gain in function.
Modafinil

For patients who continue to experience daytime sleepiness while using CPAP therapy at night, a drug called modafinil, trade name Provigil, may help. Modafinil works by increasing dopamine levels. This drug has a stimulant effect on the brain without acting like an amphetamine. It promotes activity of the neurotransmitter serotonin and inhibits activity of the neurotransmitter GABA and has been shown to improve scores on a sleepiness index by an average of 40%. Potential side effects of modafinil include anxiety, headache, nausea, and nervousness. Modafinil may also cause back pain, dry mouth, indigestion, diarrhea, dizziness, tingling or burning sensations, and swelling. Side effects have been reported in up to 36% of trial participants.

Spironolactone

Patients who experience supine hypertension (elevated blood pressure when lying down) may develop worsening sleep apnea symptoms due to fluid retention caused by this condition. A diuretic drug called spironolactone, trade name Aldactone, reduces blood pressure by lowering levels of aldosterone, an adrenal hormone that causes the kidneys to retain sodium and water. In one study, spironolactone reduced occurrences of sleep apnea by 45%. Spironolactone is a potassium-sparing diuretic and can alter certain mineral levels. About 10% of patients who take this drug accumulate excess potassium and 12% of patients develop low sodium levels. Side effects include muscle paralysis and heart problems. This drug may also impair kidney function, worsen Parkinson's symptoms, and decrease testosterone levels.

Serotonin-Influencing Drugs

Fluctuating levels of the neurotransmitter serotonin may contribute to sleep apnea. At night, levels of serotonin, which signals throat muscles to relax, normally decline, particularly during the transition from wakefulness to sleep, increasing risk of airway constriction. Serotonin also influences breathing control centers in the brain. Serotonin-enhancing drugs, such as buspirone (Buspar), fluoxetine (Prozac), and paroxetine (Paxil) may help alleviate some symptoms of sleep apnea. Animal studies have shown promising results with buspirone for improving irregular breathing patterns. A clinical trial used a combination of the drugs fluoxetine, which activates serotonin in the brain, and ondansetron (Zofran), a drug that blocks certain serotonin receptors in the brain and peripheral nervous system that can cause anxiety and autonomic system activation. The combination therapy improved breathing during REM and non-REM sleep, reducing episodes of apnea by 40%. However, use of serotonin-enhancing drugs may not alleviate daytime sleepiness.

Potential side effects of buspirone include restlessness, nervousness, blurred vision, sweating,
dry mouth, muscle pain, difficulty sleeping, and fatigue. Side effects of fluoxetine and paroxetine include insomnia, rash, headache, joint and muscle pain, digestive disturbance, reduced blood clotting, and decreased libido. Ondansetron has been associated with side effects such as confusion, dizziness, racing heart, fever, headache, difficulty breathing, and weakness. Less commonly, ondansetron may cause urination problems, including decreased frequency, decreased volume, difficulty passing urine, and painful urination.

**Donepezil**

Sold under the brand name Aricept, this drug decreases breakdown of the neurotransmitter acetylcholine, and has been found to decrease the number of incidences of apnea and low blood oxygen per night. A clinical trial of donepezil found that it significantly decreased the time participants spent in a low-oxygen state, improved sleep efficiency, and decreased daytime sleepiness. Potential side effects of donepezil include nausea, diarrhea, muscle cramps, difficulty sleeping, and fatigue.

**Armodafinil**

The stimulant drug armodafinil, trade name Nuvigil, can reduce daytime symptoms in sleep apnea patients. In one study, participants showed faster reaction time, better problem-solving and cognitive function, and fewer errors in a driving simulation test. Potential side effects of armodafinil include breathing difficulty, chest tightness, racing heart, frequent urination, itching or burning sensations, and skin rash.

**References**

8. [http://www.med.nyu.edu/content?ChunkIID=104276](http://www.med.nyu.edu/content?ChunkIID=104276)
REM sleep behavior disorder (RBD), also referred to as REM sleep without atonia (RSWA), is a condition in which muscles fail to relax during REM sleep, instead, remaining active or contracted. RSWA is diagnosed via sleep study (polysomnogram) and is distinct from sleep walking, sleep terrors, and nocturnal panic disorder. Bed partners of patients with RSWA often describe that their partners display highly active and/or violent behavior during sleep, such as flailing limbs, dream enactment, and walking from or falling out of bed. Patients often recall their dreams, which correlate with their enactment behavior. However, rather than being aggressive in nature, patients usually report their dreams as being defensive, such as fending off an attack, as opposed to being the attacker. Though not all patients with RSWA experience dream enactment, when present, it raises the potential for injury to both themselves and their partners.

RBD is regarded as a potential early sign of MSA and other alpha-synuclein disorders. Risk for developing Parkinsonism after being diagnosed with RBD is 20% to 45% within 5 years and 45% to 55% within 12 years. MSA is the most common of the alpha-synucleinopathies to be associated with RBD, with 68% to 88% of MSA patients affected. Antidepressant use increases risk of developing RBD by 500%.

Non-Pharmacological Treatment Options

Safety First

Safety concerns dictate that the first order of treatment for patients with RBD is to injury-proof the bedroom as much as possible. Remove guns, weapons, and loose objects that could be used as weapons. Pad sharp corners of furniture. Place the mattress and box spring directly on the
floor or place a second mattress on the floor next to the bed or use bed rails around the bed to cushion or prevent falls from the bed.

**Specialized Alarm System**

To prevent injury during episodes of RBD, an alarm system that gently awakens the patient has been devised. The technique has been reported successful in patients with a history of sleep-related injury from RBD who were not responsive to medication. This technique may also prove to be preferable to prolonged use of pharmaceuticals, which cause side effects, such as daytime drowsiness, cognitive impairment, falls, and worsening of sleep apnea.

The alarm technique is feasible due to the fact that during REM sleep, the brain processes sounds in a way that is similar to the waking state. As a result, RBD patients are easy to awaken and are often responsive to verbal communication while involved in dream enactment. The system uses either a pressure-sensing pad or a cord attached to the bed by a magnet connected to an alarm. The other end of the cord is clipped to the patient's bed clothes. When triggered by movement that breaks the magnetic contact, such as the patient falling out or attempting to leave the bed, the alarm plays a pre-recorded, familiar voice speaking gently and reassuringly to the patient. Serious and minor sleep-related injuries were completely eliminated during the 36-month study period. Additionally, after the first few months, fewer interventions were necessary, indicating overall improvement in REM phases of sleep. Patients who used the alarm system also reported feeling less anxious about going to sleep.

**Pharmacological Treatment Options**

**GABA-Enhancing Drugs**

**Clonazepam** (Klonopin), a GABA-enhancing drug in the benzodiazepine family, reduces dream enactment in REM behavior disorder, or RBD. Clonazepam increases total sleep time, decreases episodes of waking up during the night, and improves sleep quality. However, clonazepam can worsen sleep apnea and should not be used in patients with sleep apnea that is not managed. Clonazepam and other benzodiazepine drugs also can cause daytime sleepiness, impair gait, and decrease activity of serotonin, which leads to mood problems such as depression. About 30% of patients who take clonazepam for RBD stop taking the drug or use a lower, possibly less effective, dose because of these disruptive side effects. For RBD patients who are able to take clonazepam, long-term use of the drug has been shown to improve the quality of non-REM sleep, increase frequency of a certain type of healthy brain wave pattern, and decrease the number of times patients wake up throughout the night.

One alternative to clonazepam is a drug called zopiclone, which was demonstrated to be effective for 73% of patients in one study and caused fewer side effects than clonazepam. Zopiclone, which is also a benzodiazepine drug, has been used for MSA patients who experience sleep apnea together with RBD and cannot take clonazepam.
Zopiclone is not commercially available in the US but is similar to ezopiclone (Lunesta) which is currently available.

**Melatonin**

A hormone the brain manufactures to control the body's day/night cycle, melatonin has shown some success in treating RBD. Levels of the hormone, which is available as an over-the-counter supplement, normally increase at night to induce sleep. In one clinical trial, melatonin reduced episodes of REM sleep accompanied by muscle activity by 30%. Benefits were sustained during the second phase of the study, meaning that those who received melatonin in the first phase showed continued improvement in spite of receiving a placebo during that phase. Melatonin did not change the pattern of eye movements or reduce certain types of muscle activity during REM sleep. However, it significantly improved the overall symptom picture in many patients and completely eliminated symptoms in some patients. Melatonin also has been shown to provide sufficient improvement without adverse side effects for some patients, while others may require a combination of both clonazepam and melatonin to obtain satisfactory results. Though there is some concern that melatonin usage might worsen orthostatic hypotension, recent evidence points to melatonin's safety with regard to blood pressure maintenance.

A drug called ramelteon, trade name Rozerem, sensitizes brain cells to melatonin and has been shown effective in treatment of REM behavior disorder in MSA and Parkinson's disease. Ramelteon improves symptoms of dream enactment and also improves the proportion of REM sleep without muscle activity. It offers an alternative to clonazepam for patients who experience side effects or for whom clonazepam is ineffective. Potential side effects of ramelteon include dizziness, sleepiness, body aches, movement or breathing difficulties, fever, and nausea.

**Dopamine-Promoting Drugs**

For some RBD patients, increasing dopamine activity can be effective. In one study, a dopamine-promoting drug called pramipexole, trade name Mirapex, improved RBD symptoms in 62% of participants. A synergistic effect also occurred in this study, as a group that received pramipexole and clonazepam in combination showed significantly greater muscle relaxation during REM sleep than with either of the drugs by themselves.

In another study, pramipexole reduced RBD symptoms by half in most participants. Patients also reported having fewer nightmares. Pramipexole's benefits may be attributed to reduced eye movements during REM sleep. However, while pramipexole also reduced leg movements during non-REM sleep, it did not reduce leg-muscle activity during REM sleep, a defining characteristic of RBD. Potential side effects of pramipexole include sudden and extreme sleepiness, sweating, lightheadedness, fainting, hallucinations, chest pain, dark-colored urine, and irregular heart rate or rhythm.

**Depressants**
A central nervous system depressant called sodium oxybate, trade name Xyrem, has been used successfully in some RBD patients who do not respond well to other medications\textsuperscript{14}. This drug also can reduce daytime sleepiness in patients with sleeping disorders. Side effects of sodium oxybate include hallucinations, confusion, shallow breathing, sleepwalking, and waking up during the night\textsuperscript{15}. It also can cause depression, nausea, numbness or tingling, tremor, and blurred vision\textsuperscript{15}. Because sodium oxybate takes effect within minutes, it must be taken while in bed and immediately before going to sleep\textsuperscript{15}. Patients usually are prescribed two doses per night, requiring users to set an alarm to awaken for the second dose. Additionally, sodium oxybate is habit-forming and can cause severe withdrawal reactions if abruptly discontinued\textsuperscript{15}.

**Other Agents**

Other agents that have been reported as helpful are imipramine (Tofranil), carbamazepine (Tegretol), triazolam (Halcion), quetiapine (Seroquel), and clozapine (Clozaril).\textsuperscript{16}

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Depression and Cognitive Impairment

Though dementia is not considered a common characteristic of MSA, cognitive impairment occurs in some patients in the form of loss of verbal memory and verbal fluency. There is considerable lack of consensus among researchers at this time regarding rate of occurrence of cognitive impairment in MSA, with results varying widely between studies and depending upon which method of evaluation is used. In one study, a test for mental status, the Mini-Mental State Examination, or MMSE, yielded 3% of participants showing signs of cognitive decline while a test called the Frontal Assessment Battery categorized 41% of participants as being cognitively impaired. Another study concluded that 72% of participants showed mild or moderate cognitive impairment, including shortened attention span, abstract thought, and delayed memory. Differences in patterns of cognitive loss between MSA-P and MSA-C patients have also been observed, with MSA-P patients tending to lose verbal memory while MSA-C patients showing difficulty in acquiring new verbal information and maintaining attention.

Anxiety, depression and emotional instability also enter the picture for MSA patients, in part due to cognitive impairment and in part from the mental and emotional stresses associated with this complex disease. MSA patients often show high scores on self-rating depression questionnaires.
Non-Pharmacological Treatment Options

Cognitive Training

Keeping the brain active through mental exercise, such as memory games or mental arithmetic sharpens memory, decision-making ability, and brain processing speed, and can help slow age-related cognitive decline. Parkinson's patients who practice mental processing exercises have been shown to improve processing speed and remain independent in activities of daily living for longer periods. Physical exercise, such as walking or a home-based exercise routine including balance training, also improves cognitive function and mental processing speed in Parkinson's patients.

Animal studies have demonstrated that exercise strengthens cell-to-cell connections within the brain and improves adaptability of brain cells in Parkinson's disease.

Repetitive Transcranial Magnetic Stimulation for Depression

A technique called repetitive transcranial magnetic stimulation (rTMS) offers non-drug, non-invasive relief for symptoms of depression that do not respond to counseling or medication. A device, about the size of a hand, is placed on the top of the left side of the patient's head, directly over the frontal lobe of the brain. It emits a magnetic field that stimulates areas of the brain that produce positive mood. A series of treatments consists of daily 37-minute sessions for 4 to 6 weeks. rTMS is considered safe and effective, with minor side effects such as scalp discomfort.

References

Neuroprotective Diet

Though the precise cause or causes of MSA are not known at this time, food choices can influence certain components of the disease process, slowing or speeding up inflammation, degenerative protein accumulation, nerve cell destruction, and decreased neurotransmitter levels.

Calorie Restriction

Eating a low-calorie diet has been shown to boost brain levels of glutamate, a neurotransmitter that contributes to motor control. Levels of glutamate, like those of dopamine, are diminished in Parkinsonism. In a preliminary animal study, 21 days of calorie restriction restored glutamate levels to normal. When initiated in the early stages or before onset of symptoms, this approach has been shown to result in less loss of dopamine-producing neurons. Primate research over the past three decades has shown that a 20% calorie-reduced diet promotes healthier aging of the brain and immune system.
Low-Protein and Protein Re-Distribution

Patients who have been prescribed the Parkinson's drugs levodopa or carbidopa may consider adopting a low-protein diet, which promotes more efficient use of these drugs that compete with dietary amino acids for absorption. Ideally, protein should be eaten an hour before or an hour after taking levodopa. Consuming the majority of your daily protein at your evening meal can also help improve effectiveness of these drugs and has been found to produce superior results to a low-protein diet in one study.

Another class of drugs for managing Parkinson's symptoms, monoamine oxidase inhibitors (MAOIs), prevents the breakdown of dopamine. However, MAOIs also prevent breakdown of tyramine, a monoamine found in certain aged and fermented foods, such as cheeses, soy sauce, pickled fish, tofu, sauerkraut, ripening produce, and beer. Tyramine, which increases blood pressure, is normally kept in check by the activity of monoamine oxidase. If tyramine levels become elevated, as from high intake of tyramine-containing foods or use of MAO inhibitors, episodes of dangerously elevated blood pressure occur. Statistically, the majority of tyramine-related high blood pressure happens from eating aged cheeses. Avoid these and all other aged, fermented, or spoiled foods. To further reduce tyrosine consumption, keep foods refrigerated and consume fresh produce within 48 hours. Use canned or frozen foods immediately after opening. Thaw foods in the refrigerator as opposed to a kitchen counter.

Anti-Inflammatory Diet

Chronic inflammation is recognized as a risk factor for numerous degenerative diseases, including heart disease, diabetes, autoimmune conditions, Parkinson's disease, Alzheimer's disease, and MSA. Inflammation in the nervous system occurs early in Parkinsonian conditions, accelerating the degeneration of dopamine-producing cells. High levels of certain types of inflammatory molecules are often present in the early stages of MSA. While the precise causes of inflammation in MSA are currently unknown, choosing a diet that is low in inflammation-promoting foods and high in inflammation-fighting foods can help manage some symptoms and slow the disease progression.

A good foundation of an anti-inflammatory diet plan starts with healthy fats. Trade trans fats, such as those in convenience foods, commercially prepared baked goods, and other foods with long shelf life for similar foods cooked with healthy vegetable oils. Prepare fresh foods at home as much as possible using olive oil. Also reduce or eliminate saturated animal fats, which promote inflammation. Eat high-omega-3, cold-water fish 2 to 3 times per week or supplement with omega-3 fatty acids. Sprinkle freshly ground flax seeds, a good vegetarian source of omega-3s, onto hot or cold cereal and drizzle flaxseed oil over salads and vegetables.

A diet that emphasizes liberal quantities of a wide variety of fruits and vegetables helps quell inflammation. Aim for 8 to 10 servings per day. Part of the anti-inflammatory benefits of fruits and vegetables comes from the soluble and insoluble fiber they contain. Fruits and vegetables also contain generous amounts of anti-inflammatory micronutrients, such as quercetin and flavonoids. Use liberal amounts of herbs and spices in your cooking. Many spices provide
considerable anti-inflammatory benefits along with being intensely flavorful. Common kitchen spices such as cinnamon, cloves, ginger, cumin, oregano, basil, parsley, rosemary, and turmeric – one of the main ingredients in curry spice – are among the highest in anti-inflammatory benefits.

**High-Antioxidant Foods**

Compounds found in certain plant foods also help protect the energy-producing parts of nerve cells, called mitochondria. Faulty mitochondrial function is thought to play an important role in the development of Parkinsonian conditions, leading to sluggish cells that accumulate high levels of oxidants, cell-damaging toxins and waste products. Sulforaphane, a compound in broccoli, cauliflower, cabbage, and other cruciferous vegetables, increases activity of cellular antioxidant defense mechanisms. Curcumin, the active ingredient in turmeric, is being studied for mitochondrial and neuroprotective benefits.

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**Constipation**

Autonomic dysfunction may slow the normal, rhythmic movement of the digestive tract, known as peristalsis, resulting in bloating, decreased appetite, and constipation. Certain drugs also inhibit peristalsis. As a result, constipation is a common problem for patients with Parkinsonian conditions.

**Non-Pharmacological Treatment Options**

**Exercise**

Physical exercise helps activate peristalsis, improves stomach emptying, and is protective against colon cancer, which is more prevalent in people who experience chronic constipation.
Stay as active as possible by walking daily, participating in group exercise classes, and enlisting the services of a physical therapist who can design an exercise program tailored to your needs and abilities.

**Hydration**

Drink at least 8 glasses, about 2 quarts, of water per day – more in warm weather or if you exercise vigorously – to ensure proper hydration of the bowel contents. A convenient way to keep track of how much water you drink is to measure out your daily allotment in the morning and use that as your drinking water throughout the day. Warm liquids will promote peristalsis, while cold liquids may inhibit proper bowel function and cause uncomfortable muscle cramping. Also, bear in mind that coffee, tea, and some herbal teas act as diuretics, drawing water out of your system that can lead to dehydration. To avoid the dehydrating effects of these beverages, drink decaffeinated coffees and teas. Alternatively, you can offset their diuretic effects by consuming extra water.

**Fiber**

A high-fiber diet is essential for promoting healthy gut function and preventing constipation. Eat plenty of whole grains, beans, fresh or dried fruit, and vegetables. Fiber supplements, such as psyllium, may help, but they could also further slow peristalsis and worsen constipation. If you use a fiber supplement, be sure to consume sufficient water to allow for the hydration and expansion of the fiber.

**Bulk-Forming Laxatives**

Psyllium, the seeds of plants in the genus Plantago, was found in a research review to be the most effective remedy for chronic constipation in older adults. High levels of soluble fiber in psyllium absorb water and swell, forming a gel that adds bulk to the contents of the intestinal tract, which stimulates peristalsis, the rhythmic muscular contractions of the colon. Psyllium is the active ingredient in the over-the-counter laxative Metamucil. When taking psyllium or other bulk-forming laxatives, it is important to consume sufficient fluids or the soluble fiber will form a hard mass, which can cause intestinal blockage. If you have swallowing difficulty, it may be easier to take psyllium in capsules rather than consuming it in a loose form mixed with water. Other, natural bulk-forming laxatives that you can incorporate into your diet include flaxseed and fenugreek.

Calcium polycarbophil, brand name FiberCon, a synthetic, bulk-forming laxative, has been found to be nearly as effective as psyllium. Calcium polycarbophil significantly decreases inflammation in the lining of the colon caused by chronic constipation and has been shown to shorten transit time through the colon and increase frequency of bowel movements in MSA patients. Potential minor side effects of calcium polycarbophil include stomach pain, bloating, and gas. Serious, though less common side effects include vomiting, difficulty swallowing, chest pain, and rectal bleeding. If these occur, seek medical attention.
**Stool Softeners**

*Docsusate sodium* and *docusate calcium* coat the surface of the stool to soften it and allow for easier passage*. However, they do not promote peristalsis, the muscular intestinal action that moves contents through the colon, so these compounds are often combined with stimulant or bulking laxatives*. Docusate is generally safe and well-tolerated*. Reported side effects include intestinal cramping, skin rash, and depletion of magnesium*.

**Non-Absorbable Sugars**

*Polyethylene glycol*, brand name *Miralax*, and *lactulose*, brand name *Cephulac*, are non-absorbable sugars that work by promoting secretion of water into the intestinal tract*. Polyethylene glycol tends to be more effective than lactulose for chronic constipation. These can occasionally cause electrolyte imbalance that can impact heart and kidney function*. Less serious side effects include abdominal cramping, nausea, bloating, and flatulence*.

**Stimulants**

*Anthraquinone*, the active ingredient in the herbs senna, aloe, and cascara sagra, stimulate peristalsis by irritating the lining of the colon. They work quickly, usually within hours, but may cause abdominal cramping. They are best used on a short-term basis, as long-term use of these drugs can cause dehydration, deplete sodium and potassium levels, and damage the nerves and muscle of the intestinal tract. As a result of these dangerous side effects, the Food and Drug Administration (FDA) has banned their use in over-the-counter laxatives*.

**Pharmacological Treatment Options**

**Serotonin-Promoting Drugs**

Serotonin-promoting drugs that have been found helpful in patients with chronic constipation include *mosapride citrate*, name brand *Mospad*, and *prucalopride*, name brand *Resolor* (not currently available in the US)*. Mosapride citrate has been found to increase transit speed of the small intestine, increase frequency of bowel movements, and decrease abdominal pain in patients with chronic constipation*.* Mosapride citrate has been found to be helpful in patients with chronic constipation due to irritable bowel syndrome (IBS)* and causes few or no side effects*.

**Fatty Acids**

*Lubiprostone*, trade name *Amitiza*, a fatty-acid compound, is the most recent drug to receive FDA approval for treating chronic constipation*. It draws water into the colon, speeding the passage of stool. Lubiprostone takes effect within 24 hours in more than half of patients and does not cause rebound constipation if the drug is stopped*. A third of participants in one trial reported a side effect of nausea, which decreased if the drug was taken with food. Other side effects of lubiprostone include headache, diarrhea, abdominal distention, abdominal pain, and
gassiness. In a review of laxatives for older adults with chronic constipation, lubiprostone was 39% more effective than placebo.

**Linaclotide**, trade name Linzess, also has been shown to be effective for constipation. Diarrhea is the most common side effect of this medication. Linaclotide begins to take effect within the first 24 hours and also relieves symptoms of cramping and bloating. In clinical trials, there was no evidence of rebound constipation upon withdrawal from linaclotide.

**Pain Management**

**Gabapentin** (Neurontin) and **pregabalin** (Lyrica), drugs that promote activity of the calming neurotransmitter GABA, have been used to help reduce pain and hypersensitivity of the intestinal tract.

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**Advanced Planning**

Because MSA is at this time a terminal disease with mean patient survival of 6 to 10 years after the onset of symptoms, patients and families should begin to make decisions regarding advanced directives, finances, hospice care, and the possibility of brain donation, if so desired.

**Advanced Directives**

Advanced directives may include a living will, the designation of a power of attorney for health care, or in some states, a combination of the two. **Living will** documents allow a patient to
specifically decide on certain treatment options, such as respiratory ventilator use, placement of feeding tubes, cardiopulmonary resuscitation (CPR), or deciding to avoid resuscitation ("do not resuscitate," or DNR) should the patient stop breathing or the heart stop beating.

Patients may complete a document designating a family member or friend to have power of attorney for health care (POA). The POA for health care, after discussion with the patient to understand the patient's wishes regarding medical treatment, grants another person the right to make decisions regarding such treatment when the patient becomes unable to do so. The POA for health care is separate from the POA for finances, and someone with POA only for health care may not make any decisions regarding patient finances.

In some states, a document may be available that combines both designation of a POA for health care and concrete decisions regarding certain medical procedures, even noting patient preferences for things the patient may want when near death, such as favorite music, prayers, rituals, or pastoral visits.

**Palliative Care/Hospice**

Hospice care may differ from place to place. Several hospice agencies may be available for patients in each city or region. Patients and families should become familiar early on with the hospice care in their area. An evaluation for the appropriateness of hospice is done by a home visit. Patients may be re-evaluated as conditions deteriorate. Many hospice agencies accept Medicare and private insurance payment, and other funding may be available.

Hospice services are usually made available if the patient has a prognosis of survival of less than 6 months. If patients survive beyond 6 months, hospice won't be discontinued, though hospice medical director periodically reviews each patient's case. Once a patient is enrolled in a hospice program, the agency will cover anything related to the terminal illness, including medical equipment and symptom management. Hospice agencies can provide nursing visits for evaluation and medication management, home health aides for bathing and hygiene, and even chaplain services if desired. Bereavement counseling is available to family for up to 13 months after death.


**Brain Donation**

Because MSA is a rare disease with no cause, cure, or specific tests for definitive diagnosis, many patients may wish to donate their brains for MSA research. The agencies that receive the brain will send the family a report to confirm the diagnosis once testing is completed. Brain donation requires a specific protocol for preservation of the brain until it is harvested, a process that must be done within 24 to 48 hours after death, in most cases. Because timing is critical, arrangements for brain donation and harvest should be in place before the patient is near death.
The Brain Support Network provides valuable support and resources to guide patients and families in developing a plan for brain donation. For details, please see the following link: https://www.multiplesystematrophy.org/resources/brain-donation-information-for-msa-patients