

Multiple System Atrophy: What You Need to Know

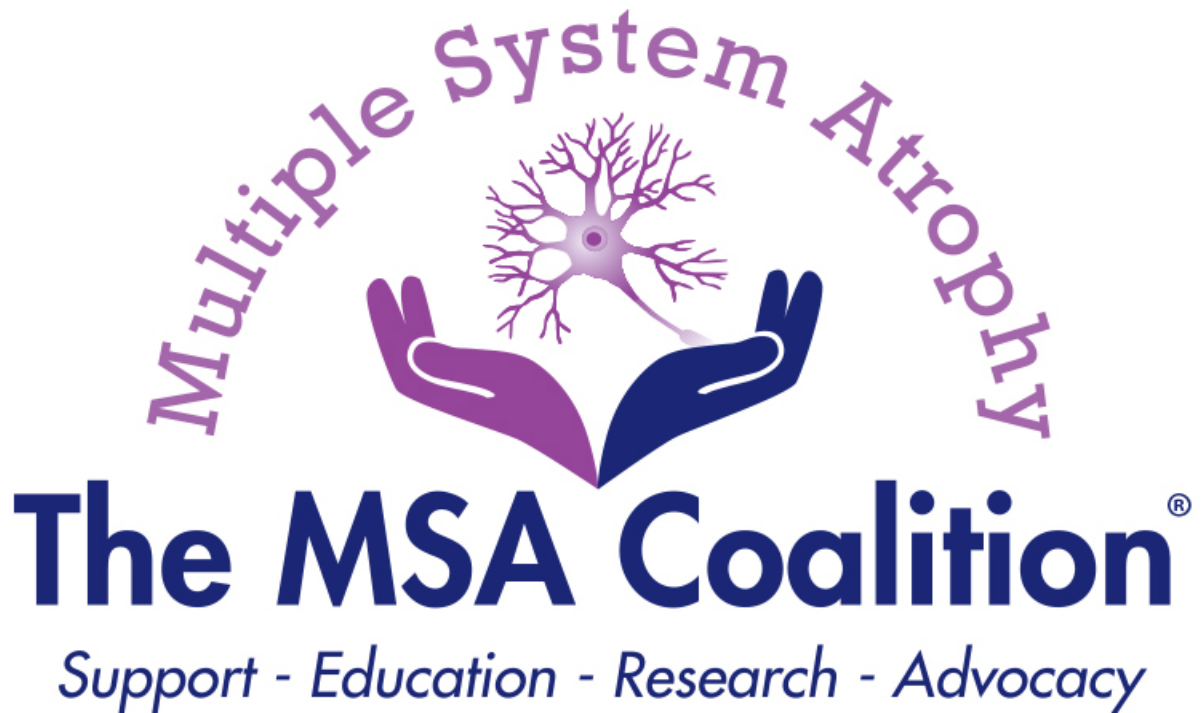


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Overview

Multiple system atrophy, or MSA, is a rare, degenerative neurologic condition that affects both men and women, usually starting in the 50's or early 60's¹. MSA is considered a type of parkinsonism but with more widespread effects on the brain and body. The condition was first identified in 1962 and named Shy-Drager syndrome for two physicians who reported patients who showed a combination of Parkinson-like movement disorders and problems with the autonomic, or body-regulating division of the nervous system².

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 dopamine⁴, 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, your brain's balance and coordination centers, and the autonomic nervous system, which controls your body's automatic, or regulating functions, such as blood pressure, digestion and temperature.

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 – support cells that maintain the health of neurons and which outnumber neurons by 10:1⁵. Additionally, some of the glial cells affected in MSA produce myelin, the fatty substance that insulates neurons⁶.

Types and Symptoms

Two forms of MSA, are recognized, according to whether parkinsonian or cerebellar symptoms predominate¹. Both types involve autonomic dysfunction, or dysautonomia. Autonomic symptoms usually appear first, though either motor symptoms or autonomic symptoms may appear first in the parkinsonian type⁷.

- MSA-P produces Parkinson-like symptoms, including a slow, shuffling gait, rigid muscles, slurred speech and lack of facial expression. Patients with MSA-P may also develop a form of tremor known as resting tremor, which occurs when they are still and disappears when they are moving.

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 and 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

(Overview, cont'd.)

assistance with daily activities as early as 5 years after diagnosis and others are able to remain independent for 20 years¹.

- MSA-C is characterized by progressive loss of coordination and balance; functions controlled by the area of the brain known as the cerebellum. MSA-C patients may experience a form of tremor known as action tremor, which occurs when they reach for an object. Muscle weakness associated with MSA-C can lead to slurred speech and problems swallowing. This form of MSA can appear as early as the 20's or not until the 60's¹.
- Dysautonomia 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 orthostatic hypotension. Conversely, blood pressure may be excessively high when lying down⁸. Loss of bladder or bowel control, abnormal sweating, sexual impotence in men and sleep disturbances, including sleep apnea, and flailing movements during sleep also occur.

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 lab 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, or fMRI, shows activity levels in the brain and can demonstrate areas of impaired brain function⁹.

Additionally, by applying sensitive pattern recognition techniques to certain MRI studies, medical science is becoming increasingly better at teasing apart the early signs of MSA from Parkinson's disease and other neurologic conditions with great accuracy¹⁰.

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 MSA¹¹.

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. Parkinson's drugs also lower blood pressure and may worsen orthostatic hypotension symptoms dizziness and fainting episodes¹.
- 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 pressure¹. Sleep apnea devices known as CPAP, or Continuous Positive Airway Pressure machines can help with

(Overview, cont'd.)

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 disability¹².

Additionally, many MSA patients succumb to secondary conditions of the disease, including pneumonia from aspirating food or saliva into the bronchial tubes, or pulmonary embolism – a blockage of the artery to the lung – due to apnea and blood pressure regulating problems¹³. As such, these therapies are valuable as a way to closely monitor functions such as blood pressure and swallowing.

Prognosis and Outlook

Prognosis is currently guarded, with most MSA patients passing away from the disease or its complications within 9 years of diagnosis³. 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.

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Differential Diagnosis

A complex disease process with many symptoms that overlap those of other health conditions, Multiple System Atrophy poses a considerable diagnostic challenge to doctors and medical researchers. Though much remains to be learned, ongoing research efforts and advancements in biotechnology continually bring science closer to understanding the causes of MSA. As an informed patient, your knowledge can help you provide your medical team with vital information at the earliest possible stages to ensure that you receive the most accurate diagnostic and management care.

MSA affects three main areas of the nervous system: the motor portion of the brain where Parkinson's disease originates; the balance and coordination centers of the brain, located in the cerebellum; and the autonomic division of the nervous system, which regulates automatic activities such as blood pressure, heart rate, sexual function, digestion and elimination. The predominant symptoms and course of the disease can vary from person to person, with autonomic signs appearing first in some, while for others, Parkinson-like or cerebellar signs are the first to manifest. Your doctor will combine your health history and physical examination findings with imaging studies and laboratory tests to arrive at a diagnosis and to gauge your progress throughout the course of your treatment.

MSA is considered a Parkinsonian condition, a group of hypokinetic, or slowed-movement disorders, including Parkinson's disease. A common underlying feature of Parkinsonian conditions is deposits of a protein called alpha-synuclein. This protein accumulates within the nervous system, impairing ability of nerves to function.

MSA-P and Parkinson's Disease

Symptom-wise, both MSA and Parkinson's disease cause slowness of movement with rigid posture, tremor and unstable, shuffling gait. However, MSA may be distinguished from Parkinson's disease in certain notable ways. In some MSA patients Parkinson-like symptoms occur only on one side of the body, while true Parkinson's disease affects both sides. Postural instability usually manifests earlier and progresses more rapidly in MSA than in Parkinson's disease. A type of tremor of the hands that is characteristic of Parkinson's disease, known as a pill-rolling tremor, does not occur in MSA patients¹.

- **Progressive Supranuclear Palsy (PSP)**

This Parkinsonian condition is characterized in the early stages by walking difficulties and frequent falls that occur along with other motor symptoms of Parkinson's disease. Difficulty moving the eyes up and down or keeping the eyelids open are distinctive features of PSP and may mimic certain cerebellar symptoms of MSA that involve eye movement. Speech and swallowing problems are also common in PSP².

- **Dementia with Lewy Bodies**

A form of Parkinsonism in which cognitive impairment and hallucinations occur along with the classic Parkinsonian signs of slow movement, rigid posture, unstable gait and tremor. Dementia with Lewy Bodies, or DLB, like Parkinson's disease and MSA, is characterized by deposits of degenerative alpha-synuclein proteins, called Lewy Bodies, in the brain. However, in Parkinson's disease Lewy bodies accumulate within neurons, large cells that transmit the brain's messages, while in MSA Lewy bodies are deposited in support cells, known as glial cells, which outnumber neurons by a factor of 10:1.¹⁴ In

MSA, a form of cognitive impairment may occur that manifests as sudden bursts of emotion, such as anger, irritability or tears that are disproportionate to the situation. The cognitive impairment of MSA is distinct from that of DLB in that it is seen as a form of clinical depression as opposed to dementia. DLB is distinguished from Parkinson's disease, which can involve a form of dementia, by the order in which symptoms occur. In DLB, dementia occurs prior to or concurrently with movement symptoms while in Parkinson's disease, if dementia develops, it happens late in the disease process³.

- **Corticobasilar Degeneration (CBD)**

This Parkinsonian condition involves dementia of the frontal lobes, where higher reasoning occurs, and temporal lobes, which process memory, together with a Parkinson-like movement disorder. Either set of symptoms can occur first. Most patients eventually develop both types of symptoms with up to 3 years lag time between initial onset and the development of both sets of symptoms¹⁵.

Multiple Sclerosis

Though not a Parkinsonian condition, multiple sclerosis can involve cognitive impairment and should be distinguished from cognitive effects of MSA. One study on cognitive impairment in MSA found that 41 percent of participants demonstrated impairment in higher brain functions such as abstract reasoning and maintaining attention⁴. These may overlap with similar symptoms that occur in about 50 percent of patients with multiple sclerosis, or MS⁵. Brain imaging studies, including MRI can be used to differentiate the patterns of white matter destruction typical of multiple sclerosis from those of MSA.

MSA-C and Spinocerebellar Ataxia

When the cerebellum becomes affected in MSA, patients experience a type of ataxia, or uncoordinated, unbalanced movement. Cerebellar ataxia affects gait, though in a different way than the unsteady, shuffling gait of Parkinson's disease. It can also include uncoordinated movement of the arms and hands, muscles of speech and impaired ability to track the eyes through space and to coordinate eye movement with movement and positioning of the body, a condition known as cerebellar oculomotor dysfunction⁶. Other conditions that can cause ataxia include stroke and multiple sclerosis⁷.

Cerebellar symptoms of MSA may overlap with a group of more than two dozen cerebellar disorders known collectively as spinocerebellar ataxia, or SCA. Like MSA, SCA conditions tend to progress rapidly⁸. SCA is generally distinguished from MSA in that it is a genetically inherited disorder, while MSA usually does not run in families. However, some studies have shown that there may be a recessive gene for MSA⁹.

Autonomic MSA Symptoms and Pure Autonomic Failure

Your autonomic system controls the automatic functions of your body such as heart rate, breathing, digestion and elimination. Numerous autonomic disorders can develop in MSA and each one must be separately evaluated to rule out a range of other conditions with similar symptoms.

In men, often the first symptom of MSA to appear, and which affects virtually all male MSA patients, is erectile dysfunction. This is soon followed by urinary incontinence, which occurs in both men and women¹⁰. Because of the age at which MSA manifests, these genitourinary conditions are often initially misconstrued as being a part of the normal aging process. As a result, patients tend to delay seeking medical care until the disease progresses and other symptoms appear.

Another hallmark of autonomic dysfunction in MSA is orthostatic hypotension. In this condition blood pressure, which is supposed to increase when you stand up from sitting or lying down, remains low, causing dizziness, falls and injuries. Nerve supply to the heart may also be compromised as part of the autonomic picture of MSA, contributing to orthostatic hypotension by failing to increase heart rate to move blood to your head as you sit up from a reclined position or stand from a sitting position.

Your body may become unable regulate its temperature by losing its ability to initiate the sweat response. Additionally, breathing muscles may be affected, resulting in periodic episodes of labored, gasping type of breathing known as stridor¹¹.

Autonomic symptoms of MSA can mimic those of an autonomic disorder known as pure autonomic failure, or PAF. However, PAF is considered a milder, less disabling condition than MSA¹². PAF can also be distinguished from MSA in that it will not be accompanied by Parkinsonian or cerebellar symptoms.

Sleep Disorders

Decreased sleep efficiency affects more than half of MSA patients¹³. Disordered REM sleep, known as REM behavior disorder, or RBD, affects up to 90 percent of MSA patients and may occur before motor symptoms show up. Some MSA patients also experience periodic limb movements and restless leg syndrome. Obstructive sleep apnea – characterized by longer than normal pauses between breaths – and RBD occur in both MSA and Parkinson's disease. However, a sleep evaluation study can help rule out other potentially independent or unrelated causes for sleep problems.

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Evaluation Methods

A thorough history and clinical neurologic evaluation form the foundation upon which your doctor will make important recommendations for further testing procedures. Evaluation may be an ongoing process as symptoms and treatments progress and can include a wide range of imaging, laboratory and other testing procedures. Providing your doctor with the most accurate and complete symptom and health history information to the best of your ability will help ensure you receive the most efficient and precise diagnostic care.

Imaging Techniques

- **MRI**

Magnetic resonance imaging, or MRI, shows areas of brain atrophy. One such study compared MRI's of patients with MSA, Parkinson's disease and a Parkinsonian condition known as progressive supranuclear palsy, or PSP¹. Researchers observed that areas of the brain most commonly involved in Parkinson's disease showed significantly greater atrophy in MSA and PSP patients compared to Parkinson's patients. Atrophy was also noted in the cerebellum and brainstem of MSA and PSP patients but not in Parkinson's patients.

Specialized types of MRI may be used to monitor the disease progress or to assess the effects of a particular therapy. Diffusion weighted MRI shows the movement of water through the brain; higher or lower than normal levels of water indicate dead or dying brain tissue². Normal results on diffusion MRI point toward a diagnosis of Parkinson's, while abnormal results indicate possible MSA, progressive supranuclear palsy (PSP) or corticobasilar degeneration (CBD)³. One study notes that on diffusion-weighted MRI 90 to 100 percent of patients with MSA and PSP show a specific pattern of atrophy within a motor portion of the brain known as the putamen that doesn't show up in Parkinson's disease³. A type of MRI called neuromelanin MRI detects nerve cells in a darkly pigmented portion of the brain involved in motor control called the substantia nigra. Degeneration of this brain structure occurs in both Parkinson's disease and MSA. At least one study has reported the ability of neuromelanin MRI to distinguish MSA from Parkinson's disease⁴.

- **PET Scan**

Positron emission tomography, or PET scan, a type of imaging technique that measures physiological functions in the brain, such as metabolism (energy utilization) and neurotransmitter activity, can help differentiate cerebellar MSA from SCA by showing patterns of low metabolic activity. A form of PET scan known as F-FDG PET scan is highly sensitive for detecting atypical Parkinsonian syndromes such as MSA³

- **Ultrasound**

Your doctor may also recommend a study known as transcranial ultrasound to evaluate structures in your brainstem that use the neurotransmitter dopamine³.

Medication

If your predominant symptoms are those of Parkinson's disease and you have had MRI and PET scan

studies that show a potential Parkinsonian condition your doctor may suggest that you take a Parkinson's drug to help raise levels of the neurotransmitter dopamine³. In about 30 to 60 percent of MSA patients, these drugs offer relief of symptoms; however, their benefits soon fade. By contrast, Parkinson's patients generally respond to these drugs for longer spans of time⁵.

Autonomic Testing

Autonomic function tests can help your doctor tell whether these symptoms are stemming from MSA, spinocerebellar atrophy or Parkinson's disease. These tests are painless and noninvasive and modern testing methods are able to detect autonomic dysfunction that early stages before you notice symptoms. Autonomic tests general reveal mild failure in Parkinson's disease, with sweating and temperature regulating problems in the later stages. MSA and pure autonomic failure involve severe and more generalized autonomic failure. Autonomic degeneration in Dementia with Lewy Bodies is of an intermediate degree⁶.

- **Tilt Table Test**

A tilt table test for orthostatic hypotension measures your blood pressure while you lie on a table that moves you from lying down to an almost standing position⁷.

- **Electrocardiogram**

An electrocardiogram (EKG) will reveal patterns of electrical supply to your heart⁷.

- **Quantitative Sudomotor Autonomic Reflex Test**

A sweat test called the Quantitative Sudomotor Autonomic Reflex Test (QSART), measures your ability to perspire. This three-part test measures resting skin temperature, sweat output at rest, and sweat output in response to a chemical stimulant. Electric pads placed on the skin deliver the chemical to the sweat glands, generating a warm sensation. Sweat output is measured and analyzed via computer program to compare sweat production to the degree of sweat gland stimulation⁸.

- **Gastric Emptying**

If you experience symptoms of early fullness before finishing a meal or nausea after small amounts of food a test to measure the speed at which your stomach empties, called a gastric emptying or gastrointestinal mobility test may be needed⁹.

- **Ultrasound**

If you have symptoms of urinary frequency, urgency or incontinence diagnostic Ultrasound helps determine if your bladder is not emptying completely⁹.

- **PET and SPECT**

PET and SPECT(single-photon emission computed tomography) scans can determine whether problems with nerve supply to your heart are showing a pattern consistent with either MSA or Parkinson's disease. PET scans are also used to determine whether and to what degree there is inflammation in the brain³.

Sleep Studies

If sleep disorders such as obstructive sleep apnea are part of your symptom picture a laboratory sleep evaluation called a polysomnograph may be recommended. Rapid eye movement, or REM, sleep disorder associated with Parkinsonian diseases has been evaluated effectively with the help of recent advances in diagnostic ultrasound, PET and SPECT scans¹⁰.

Blood Tests

Your doctor may order tests to determine your levels of norepinephrine, a chemical that functions as both a hormone and neurotransmitter. Norepinephrine stimulates your heart and low levels may contribute to orthostatic hypotension by keeping your heart rate from elevating sufficiently to increase your blood pressure when you stand. Your doctor may also recommend blood tests for markers of immune function and inflammation, which are thought to play a part in early stages of MSA¹¹.

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Orthostatic Hypotension: Non-Pharmaceutical Treatment Options

Also known as OH, orthostatic hypotension is a condition in which your autonomic system, which controls the automatic functions of your body, loses the ability to properly regulate your blood pressure when you move from sitting or lying down to standing, or when you change positions quickly. As a result, people with OH suffer sudden and dangerous drops in blood pressure. Doctors define OH as a 20 mm Hg drop in systolic blood pressure – the upper number of the blood pressure ratio, or a 10 mmHg decrease in diastolic pressure – the lower number of the blood pressure ratio, within three minutes of standing up from sitting or lying down⁹. Other everyday activities that elicit an increase in blood pressure, such as digesting food, lifting heavy objects and defecating can also bring on an episode of OH.

The main symptoms of OH 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 standing¹. OH is common in MSA, affecting about 75% of patients¹. By comparison, up to 58 percent of Parkinson's disease patients and 10 to 30 percent of the aging population at large experience orthostatic hypotension¹.

Lifestyle Changes

Numerous non-drug methods may help prevent or manage OH symptoms. If you are experiencing OH, a few lifestyle changes may be in order, including moving more slowly and carefully than you 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 day². Rearranging your activities for afternoons rather than mornings, when OH symptoms are more pronounced, may result in fewer episodes of OH². Also, avoid heavy lifting².

Compression Stockings

Preventing blood from pooling in your legs when you stand up can keep your 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 OH comes from research conducted by the aerospace industry. OH affects astronauts that 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 orthostatic hypotension upon their return to Earth. One study showed that inflatable compression suits and specially designed compression garments increase astronauts' blood pressure and improved their ability to perform tilt tests without experiencing orthostatic hypotension³. 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^{4,5}. 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 OH in some MSA patients⁶. Increases of over 40 mmHg in systolic pressure have been observed within 20 minutes of rapidly drinking 480 mL, or about 16 ounces⁶.

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 participants with MSA who underwent a tilt test after consuming 450 mL of clear soup⁷. Similarly, sugary drinks have the opposite effect, lowering blood pressure instead of raising it⁸.

Salt and Kidney Function

Eating a high-salt diet is an effective way to raise your blood pressure and is recommended for patients with OH provided there is no history of kidney disease. Check with your doctor before implementing any dietary change.

OH causes the kidneys to function differently, in ways that perpetuate OH, 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 OH symptoms¹⁰.

Elevation of Head of Bed

Raising the head of your bed by 10 to 30 degrees while you sleep can raise your standing blood pressure and help offset the low blood pressure effects of OH⁹. You may need to do this regularly for a few weeks before you see noticeable benefits⁹.

Leg Crossing

Crossing your legs can help with OH by decreasing circulation to the legs, thereby maintaining higher blood volume and blood pressure in your head¹¹. 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 percent¹², resulting in improved blood flow and oxygenation to the brain and less risk of dizziness, falling and other complications of OH. Contracting your leg, buttock and abdominal muscles while using the leg crossing method can help maintain blood flow in your legs while still increasing blood supply to your head^{13,14}.

Reducing Medications

Dopamine drugs for Parkinson's symptoms and medication for high blood pressure may worsen OH symptoms and you may be required to reduce or discontinue those medications in order to effectively manage OH⁹.

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Orthostatic Hypotension: Pharmaceutical Treatment Options

Medication therapy for OH is highly individualized. As opposed to bringing your blood pressure up to standard normal values, which may not be realistic or necessary,¹ the goal is to arrive at the proper drug and dosage level that most effectively manages your OH symptoms.

Adrenal-Supportive Drugs

One of the mainstay medicines for OH is fludrocortisone, trade name Florinef. This drug is a synthetic adrenal corticosteroid hormone that increases blood volume and blood pressure by making your body retain sodium, which increases 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 urine². However, fludrocortisone's blood pressure-raising effects can cause your blood pressure to become elevated while you are supine (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^e. Potential side effects of fludrocortisone include difficulty sleeping, dizziness, headache, sweating, indigestion and nervousness³.

Midodrine, trade names Amatine and Gutron, elevates blood pressure by making your arteries and veins more sensitive to adrenaline, an adrenal gland hormone that causes blood vessels to contract. In a review of research studies conducted on midodrine, researchers found that it increased standing blood pressure by an average of 21.5 mmHg⁴. Midodrine increased systolic blood pressure – the top number of the blood pressure ratio, signifying pressure in arteries during heart contraction – by an average of 4.9 mmHg⁴. Study participants reported significant improvement in their symptoms⁴. Potential side effects of midodrine include difficulty initiating urination, urinary urgency, elevated blood pressure when supine (lying down), itchy scalp and goose bumps on the skin⁴. Midodrine can also cause blurred vision, dizziness, fainting, headache and pounding in the ears⁵.

Droxidopa, a newer drug that is being used for managing OH, is a chemical that your body converts to two neurotransmitters: norepinephrine and adrenaline. This versatility allows Droxidopa to work both in the brain, where it acts on blood pressure regulating centers, and the body, where it influences the heart, blood vessels and other organs to increase standing blood pressure⁶.

A clinical trial that included patients with MSA and pure autonomic failure found that Droxidopa improved OH symptoms in 78 percent of participants and completely eliminated symptoms in 44 percent of participants⁷. Drops in supine-to-standing blood pressure improved by 40 percent⁷. In another study, symptoms such as dizziness, lightheadedness and blurred vision also improved. Additionally, Droxidopa did not cause an increase in supine blood pressure. Droxidopa has been in use since 1989⁸ 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 fainting⁸ these instances may have been related to disease severity as opposed to side effects caused by Droxidopa⁸.

The herb yohimbine, which stimulates production of adrenalin and activates adrenalin receptors¹³ has

been shown to prevent blood pressure from dropping upon standing from lying down by more than 10 mmHg¹¹. Potential side effects of yohimbine include racing or irregular heartbeat, anxiety, tremor, or confusion. Allergic reaction to yohimbine may cause swelling of the throat and difficulty breathing.

Atomoxetine, trade name Straterra, helps keep adrenalin in circulation. It is particularly useful if, as for most MSA patients, your OH stems from degeneration of blood pressure control centers in your brain but adrenalin receptors throughout your body remain intact⁹. Potential side effects of atomoxetine include acid indigestion, cough, urine retention, urinary incontinence, constipation, nausea, chest tightness, difficulty sleeping and fatigue¹⁴.

The drug pyridostigmine inhibits the breakdown of the neurotransmitter acetylcholine, the main neurotransmitter of the autonomic nervous system. By doing so, it stimulates the adrenal glands to release adrenalin⁹. Pyridostigmine produces a significant increase in standing blood pressure. It also helps avoid the problem of elevated supine blood pressure by promoting adrenalin production only during times of activity and not when you are sedentary⁹. However, pyridostigmine has been found to be less effective in severe forms of OH⁹. In a comparison study of yohimbine with pyridostigmine in MSA, Parkinson's disease and pure autonomic failure patients with severe autonomic failure, yohimbine raised standing blood pressure an average of 11mmHg and reduced OH symptoms¹³ while pyridostigmine raised blood pressure by an average of 0.6 mmHg with no improvement in symptoms. Potential side effects of pyridostigmine include extreme muscle weakness and twitching, slurred speech, vision problems, severe vomiting or diarrhea, anxiety and seizure¹⁰.

Brain Neurotransmitter Activation

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 OH symptoms⁹. 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 disease⁹.

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 OH symptoms⁹. Disadvantages of recombinant erythropoietin are that it must be delivered by injection three times per week and is costly⁹.

An alternative to recombinant erythropoietin is a drug called Desmopressin, or DDAVP, a synthetic form of the blood pressure-raising hormone vasopressin⁹. Desmopressin is injected at bedtime and is safe to use if you have elevated supine blood pressure. However, this medication can cause low sodium levels⁹.

Other Drugs and Supplements

Ocreotide, 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 midrodrine for improving prolonged standing ability⁹. Octreotide can be used in conjunction with midrodrine; however, it must be injected⁹. 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 non-steroidal anti-inflammatory and the supplement potassium chloride raise blood pressure, on average, more than 10 mmHg¹¹. Potential side effects of indomethacin may include acid indigestion, nausea and vomiting, and diarrhea. Potassium chloride side effects may include diarrhea, nausea and vomiting¹⁸.

Patients have also reported improvement in symptoms with a combination of the herbs camphor and hawthorn berry¹¹. The herbal combination has been tested in clinical trials and found effective for some patients with OH¹⁷. These substances are generally considered safe and well-tolerated¹⁷, though some people have experienced fatigue, nausea or sweating from taking hawthorn¹⁹.

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Neurogenic Bladder: Non-Pharmacological Treatment Options

Your 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 your 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 urination⁴. Symptoms such as incontinence, leakage, urinary frequency and urgency affect up to 96 percent of MSA patients and are often one of the first signs to appear². Urinary problems that go untreated can lead to infections, kidney damage and kidney stones¹. 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. You may be unaware that your bladder is not emptying fully and only suspect a problem when you find yourself having to void again within minutes. An ultrasound study will determine whether your 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 is a prevalent condition in MSA patients, affecting up to 77 percent of patients who have urinary symptoms². 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.

Your pattern of urinary symptoms forms an important distinguishing feature that helps your doctor differentiate between MSA and Parkinson's disease. In Parkinson's disease 58 percent 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 Parkinson's disease than they do in MSA; usually 5 or more years after diagnosis compared to less than two years post-diagnosis in MSA patients⁷. MSA patients generally experience problems with both urine storage and voiding⁴.

Intermittent Self-Catheterization

If ultrasound evaluation reveals that there is residual volume of 100 milliliters, or more than one-third of your bladder capacity, your doctor may recommend intermittent self-catheterization¹. For this procedure, you or a caregiver will insert a flexible plastic tube, called a catheter, into the urethra and up to the bladder to allow residual urine to drain. A regular schedule of catheterization immediately upon awakening in the morning, every three to four hours throughout the day and evening and just before you go to bed at night³. 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 amounts of time.

Permanent (Foley) Catheter

You might require a permanent, indwelling catheter, known as a Foley catheter, if intermittent self-catheterization becomes ineffective or inconvenient for you. This type of catheter has 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 it from shifting⁸.

Maintenance of a Foley catheter requires careful attention to hygiene and catheter function. You will need to visually check the collection bag every 1-2 hours to make sure there are no blockages. You will also need to wash the area using sterile equipment and technique at least twice each day and your Foley catheter must be changed every two to four weeks. This is a simple procedure that can be performed at home or at your doctor's office by a nurse or trained caregiver⁹. Twice per year, or as needed, your doctor will order a full urinary work-up, including ultrasound imaging and x-rays of the bladder to monitor your bladder health while using the Foley catheter⁸.

Bladder Diary

To help ensure that your self-catheterization program is successful, you'll likely be advised to keep accurate records of your fluid intake, voiding schedule and amount of urine collected. It is recommended to consume about 1.8 liters of fluid and to void approximately 1.6 liters of urine per day⁴. You can accomplish this by drinking 400 milliliters with each meal and an additional 200 milliliters at 10:00 a.m., 2:00 p.m. and 4:00 p.m.⁴. To avoid the need for catheterization during the night, restrict fluid consumption after dinner to sips⁴.

Bladder Retraining

In some instances an overactive bladder wall muscle can be retrained by carefully timing your catheterization intervals. If your doctor recommends trying this technique, after taking initial recordings of time and urine volume collected, you'll gradually lengthen the intervals so that your bladder holds more urine with fewer inappropriate contractions of the bladder wall⁴. You might start by setting your interval time for 15 minutes longer than your previously established interval time⁵. If you feel the urge to urinate before the extra 15 minutes is up attempt to distract yourself by contracting your pelvic floor muscles. These contractions, known as Kegel exercises, stop the flow of urine and also inhibit the detrussor muscle. Start by contracting these muscles for 3 to 5 seconds, then rest for 3 to 5 seconds. Gradually build up to 10-second contractions. Crossing your legs or focusing on breathing slow, regular breaths can also help you reach your goal interval time.

Surgical Options

If intermittent self-catheterization becomes problematic or ineffective your doctor may recommend a permanent form of catheterization known as a suprapubic catheter¹. In this procedure, a catheter is inserted into the bladder through an incision made just above the pubic bone. Your bladder will drain through the catheter into a collection bag⁶. You or a caregiver will need to replace this catheter at home every 4 to 6 weeks⁶. Particular attention to proper care of the skin around the catheter is important in

order to prevent infection. You 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 your bladder and situated so that the tube does not become kinked.

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Neurogenic Bladder: 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 prostatic enlargement propiverine combined with certain prostate medications has proven effective for improving urine storage capacity².

Oxybutynin

An anticholinergic drug called oxybutynin decreases overactive detrusor muscle and can be used in conjunction with an indwelling catheter³. Oxybutynin helps prevent bladder leakage and backup of urine into the kidneys¹. 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 form⁴. You can also take oxybutynin as a transdermal patch, from which the drug is absorbed through the skin⁴. The patch form of oxybutynin causes fewer side effects than oral oxybutynin.

Other anticholinergic drugs used for neurogenic bladder include:

Tolterodine, a drug that is highly specific to the bladder, giving it a lower overall side effect profile than other anticholinergic drugs⁹.

Solifenacin, an increasingly popular newer-generation anticholinergic for use in women¹⁰ and also particularly effective in elderly patients and those with cognitive dysfunction.

Darifenacin, a drug that is safe for patients with heart problems or cognitive impairment⁴.

The most common side effect associated with anticholinergic drugs and one of the major reasons patients discontinue taking anticholinergic drugs⁵ is dry mouth. In general, extended release forms of anticholinergic drugs are associated with lower incidence of dry mouth due to lower peak blood levels compared to immediate release forms. A comparison study between propiverine and oxybutynin found that propiverine was less likely to cause dry mouth⁸. Other anticholinergic side effects include urinary retention – which affects men more than women⁶, dry eyes, and constipation⁷.

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 urination reflex in spinal nerve injury¹¹. In another study, nitric oxide was found to relax the muscle of the bladder neck¹².

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 sildenafil¹³, trade name Viagra; tadalafil¹³, trade name Cialis¹⁴; and verdanafil, 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 urination¹⁵.

Tadalafil in combination with tamsulosin, trade name Flomax – a drug used to treat benign prostatic hypertrophy, demonstrated a synergistic effect that relaxed the prostate and the bladder neck to a greater degree than either drug by itself, in a preliminary study¹⁴. 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 dysfunction¹⁶.

A clinical trial of tamsulosin found that it increased urine flow rate by an average of 45 percent and decreased residual urine volume by 30 percent in patients with intact detrusor muscle function¹⁷. 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 urination²¹. Tamsulosin may also cause chest pain, dizziness, fainting and prolonged or painful erections²¹.

Potential side effects of PDE-5 inhibitors include headache, flushing, stomach upset, and nasal congestion²⁰. There have also been occurrences of sudden, irreversible hearing loss following use of these drugs²⁰.

Baclofen

This GABA-promoting drug has been found to help calm overactive bladder, improve urinary sphincter function and increase bladder capacity³. Baclofen 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 MSA symptoms¹⁸. Potential side effects include allergic reactions, such as skin rash or swelling of the lips or tongue, chest pain, hallucinations and seizure²². You may also experience sleeping problems, headache or nausea²².

Botulinum Toxin

If medication proves ineffective your doctor may recommend an injection of botulinum toxin into the bladder wall as an alternative. This therapy calms an overactive detrusor muscle and increases bladder capacity¹⁹. 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 effects⁵.

If you are unable to perform self catheterization your doctor may recommend botulinum toxin injections to temporarily paralyze the external sphincter and help with bladder emptying³. Each botulinum injection lasts three to nine months. This simple procedure is less invasive than surgery and there are minimal side effects associated with it³.

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Parkinson's: Non-Pharmacological Treatment Options

Stem Cell Therapy

Protecting healthy nerve cells and promoting the body's ability to repair and regenerate affected cells are important components in the management of Parkinson symptoms associated with this rapidly-progressive condition¹. Current Parkinson's drugs offer limited results in terms of percentage of patients who respond and duration of benefits those patients receive. To bridge this treatment gap medical scientists are actively investigating a range of potential non-pharmacological treatments, some of which have fared well in human clinical trials^{1,2}.

Stem cell therapy – the use of immature cells capable of developing into specialized cells, is emerging as a promising technique. Stem cells also produce important nerve-protective substances. A type of stem cell known as a mesenchymal stem cell (MSC) can be taken from the patient's bone marrow. MSC's secrete cellular growth factors that make nerve cells more resilient to the damaging effects of the disease process and help ailing cells recover and regenerate². They also modulate the immune system and reduce inflammation², a known contributing factor in the course of MSA. Stem cells can be either injected into the bloodstream and allowed to migrate to injured brain areas or they can be surgically transplanted into the brain, where they might differentiate into dopamine producing cells¹.

In one clinical trial, MSC injection therapy significantly improved Parkinson and cerebellar MSA symptoms. Benefits appeared early and were maintained throughout the year-long study period. Researchers noted that MSC therapy was safe and delayed disease progress while improving function in study participants compared to a control group of MSA patients. PET scans of the treatment group showed increased metabolic activity in affected brain areas, indicating more active, healthy brain function³. In an animal study, MSC therapy increased survival of cells in the substantia nigra, a motor area of the brain affected in Parkinsonian conditions, by 50 percent⁴.

Physical Therapy and Exercise

You may find that certain Parkinson-related movement problems improve with physical therapy. Treadmill training challenges you to maintain a consistent rhythm and speed, which helps improve Parkinson gait disorder⁸. In a study that used an assisted treadmill exercise in which 20 percent of the participants' body weight was supported, participants achieved significant gains in stability, balance and gait⁵. Yoga along with physical therapy has been reported to increase strength and decrease Parkinson-associated muscle rigidity⁶. Parkinson's patients who take part in physical therapy programs also develop better balance and endurance and suffer fewer falls⁷. In an animal study of advanced Parkinson's disease in which there was 90 percent loss of dopamine, a 4-week exercise program doubled the animals' running endurance compared to a control group that did not exercise¹⁶.

Mobility of the muscles of the trunk, important for turning movements, may benefit from targeted exercises that promote flexibility, range of motion and relaxation.⁸ Strength training that focuses on eccentric muscle contractions – those that occur when a muscle is lengthening and contracting at the same time, such as when you straighten your elbow – can help preserve mobility and may be more

effective than concentric strength exercises, in which muscles shorten during contraction, such as when you bend your elbow⁸. Tai Chi and Pilates exercises are thought to improve balance and posture by promoting greater sensory awareness and integration of movement⁸. Importantly, exercise also strengthens your brain and makes nerves and neurotransmitters function more efficiently, slowing the disease progress⁸.

Occupational Therapy

Fine motor skills for writing, dressing, computer use and other activities of daily living may benefit from occupational therapy. An occupational therapist can also address problems with memory and concentration. Through the use of innovative computerized activity simulators such as the Nintendo Wii gaming system, an occupational therapist can help you practice timing your movements to sensory stimuli⁹. Playing simulated games such as bowling, tennis and golf trains eye-hand coordination in an entertaining way while conserving energy for daily activities.

Speech Therapy

Problems with the muscles of speech affect 90 percent of Parkinson's patients and produce characteristic voice patterns such as hoarseness, monotone and a quiet, mumbling speech pattern. Speech can also lose cadence, with hesitations followed by rapid bursts. A form of occupational therapy known as the Lee Silverman Voice Treatment (LSVT) uses loud vocalization to strengthen respiratory muscles, increase air pressure in the throat and improve evenness of speech. LSVT has been shown to improve speech articulation and rate, swallowing ability and facial expression. Vowel pronunciation, which relies on proper coordination of the lips, tongue and jaw, is particularly helped by this technique. Additionally, LSVT improves the patient's perception of his or her voice and activates areas of the brain responsible for attention and motor function related to speech¹⁰.

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Parkinson's: Pharmacological Treatment Options

Levodopa

To help control Parkinson's symptoms your doctor may recommend Levodopa, also known by the trade name Sinemet, a chemical that is converted into dopamine in the brain. Levodopa restores depleted dopamine levels and is considered the gold standard drug for Parkinson's disease and is also used to control parkinson's symptoms in MSA patients¹.

Levodopa may also cause new movement disorders, known as dyskinesias, to appear and has been associated with a lower benefit-to-side effect ratio in MSA compared to Parkinson's disease³. A comparison study of certain brain wave patterns of Parkinson's and MSA patients' response to levodopa showed that MSA patients' on levodopa displayed a level of function similar to that of unmedicated Parkinson's disease patients².

In practice, response of MSA patients to levodopa varies widely from patient to patient, leading some experts contend that the actual percentage of patients who benefit from levodopa therapy may be close to 40 to 60 percent among MSA-P patients, with some studies reporting as high as 69 percent, as opposed to the more widely-held belief that most MSA patients are not helped by levodopa therapy⁴.

Levodopa's usefulness in Parkinsonism is limited due to the fact that the drug's effectiveness diminishes over time, with each dose gradually lasting a shorter duration⁵. As a result, symptoms begin to return between doses and, in some patients, dyskinesias appear, usually in the face, neck or limbs. In MSA the decreasing effectiveness of levodopa is compounded by loss of the cells that respond to dopamine as the disease progresses.

As a result, benefits of levodopa generally wane after two to three years in most MSA patients compared to five or more years in Parkinson's disease patients⁵. High doses of levodopa are also thought to contribute to the disease process in MSA, though at least one preliminary study has found this to be untrue⁶.

To get around levodopa's limitations and to prolong its potential effectiveness your doctor may recommend putting off using this drug for as long as possible and using the smallest effective dose that helps you function better but may not fully alleviate all symptoms⁵.

Drug manufacturers offer various formulations of levodopa and other types of drugs designed to help make levodopa more effective for long-term use. A sustained release form of levodopa offers a solution by keeping levels of the drug more constant so as to prevent the symptom fluctuations that occur toward the end of a dosing period or overnight⁵. Another drug called entacapone, trade name Comtan, prevents breakdown of the levodopa molecule, keeping it active in the brain longer and allowing for a lower levodopa dose⁵.

Potential side effects you may experience with entacapone include a change in the color of your urine to a brownish-orange color, constipation or diarrhea, dizziness, fatigue, dry mouth, nausea and stomach pain⁷. Rarely, a severe allergic reaction may occur or the drug may cause chest pain or worsening of

Parkinson's symptoms.

Dopamine Agonists

A category of drugs called dopamine agonists mimic the effect of dopamine but are somewhat less effective or specific than dopamine⁵. Dopamine agonists take longer to break down, so they stay in the brain longer, have a longer-acting effect and cause fewer of the dyskinesia side effects associated with levodopa therapy⁵.

A dopamine agonist called 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 ability to dress and use eating utensils⁸. Potential side effects of pramipexole include daytime sleepiness, dizziness, fainting, nausea, difficulty sleeping or uncontrolled movements.

Occasionally, levodopa is used in combination with a dopamine agonist called apomorphine. In one study, patients were administered levodopa, apomorphine or a combination of the two and then tested on a Parkinson's disease rating scale. Participants with MSA experienced a 12 percent improvement in motor symptoms¹⁰.

Potential side effects of apomorphine include chest pain, chills, cold sweats, confusion and dizziness. Apomorphine may also cause extreme sleepiness, mood changes, hallucinations, swelling, and worsening of Parkinson movement disorder symptoms.

Implantable Device

A drug delivery system that uses an implantable device saturated with levodopa and designed to release small amounts continuously has proven effective for up to six months with no adverse effects, in preliminary animal studies¹².

Amantadine

An antiviral drug called amantadine, trade name Symmetrel, has been found to improve mild Parkinson's symptoms. Its precise action is unknown, though it is thought to possibly promote release of dopamine by brain cells and it might inhibit acetylcholine, a neurotransmitter that activates muscles, thereby having a calming effect on parkinsonian-type tremors and other movement disorder symptoms. Potential side effects of amantadine include blurred vision, dizziness, fainting, confusion, problems with urination and swelling of the hands and feet¹³.

Antidepressants

Antidepressant drugs that increase serotonin levels, such as one called paroxetine, trade name Paxil, have also been found helpful for movement disorders associated with MSA¹⁴. Paroxetine has been shown to improve speech, swallowing and facial expression in Parkinson's disease¹⁵. Potential side effects of paroxetine include irregular heart rhythm, dizziness, nausea, balance problems, restless legs, panic attack, sexual dysfunction, insomnia, heartburn, and anxiety¹⁵.

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Cerebellar Ataxia: Non-Pharmacological Treatment Options

Lack of control of postural muscles combined with decreased coordination of the arms and legs results in a wobbly, wide-based, staggering gait that characterizes cerebellar ataxia¹. 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 affected¹.

Physical Therapy

The goal of physical therapy for cerebellar ataxia is to improve your ability to stabilize your body so that you can stand, walk and function independently for as long as possible. A thorough evaluation will help your physical therapist identify the precise areas of your balance and coordination problems in order to devise an appropriate treatment plan for you. Some exercises target receptors in your joints that tell your brain where your body parts are, a sense known as proprioception. Certain stretching techniques, resistance exercises and walking on different types of surfaces are used for this purpose. A physical therapy modality called whole body vibration, which requires you to stand on a mildly vibrating platform, has been shown to increase blood flow and nerve supply to muscles in some forms of ataxia². Vibration can also be applied to individual joints, as needed. Movement awareness therapies such as Feldenkrais, Alexander Technique, yoga and tai chi also activate the sense of proprioception¹.

Exercises for improving balance focus on activating, stabilizing and strengthening abdominal and back muscles. Your therapist may have you start in a lying position and progress to sitting, standing and walking exercises¹. Variations such as having your eyes closed, moving your head and eyes in coordination with body movements, standing on one leg or walking on two lines that are slightly narrower than your comfortable stance help train sensory feedback circuits¹. Such therapy can restore and preserve function and prevent loss due to inactivity.

Starting a physical therapy program as early as possible may improve the longterm course of cerebellar ataxia. In one study of patients with degenerative cerebellar disease significantly greater improvement in ataxia symptoms and walking speed occurred in a group that entered a physical therapy program immediately after being diagnosed compared to a group that entered the same program after a four-week delay³. Benefits have been shown to persist for up to one year after just one 4-week intensive course of physical therapy, helping patients maintain a high degree of independence in spite of disease progression⁴. Another study that focused on coordination exercises found that following through with continuous, ongoing physical therapy is a key component for maintaining functional gains⁵.

Occupational Therapy

Evaluating and training specific functional tasks related to activities of daily living with the help of an occupational therapist has been found to stabilize disability ratings and decrease depression, possibly by improving patients' independence^{7,8}. In one study occupational therapy utilizing core muscle exercises improved fine motor coordination of the arms and hands by stabilizing the trunk to prevent postural

sway⁹. Video simulation games that use eye-hand coordination or whole body coordination offer another option for cerebellar ataxia therapy. These have been found helpful in children with degenerative ataxias and can also be an effective and enjoyable way for adult MSA patients to perform exercises at home⁶.

Biofeedback

A form of biofeedback produced encouraging results in a study involving degenerative cerebellar ataxia patients. The device provided feedback information to the patient about his or her head position. Participants used the device both with eyes open and eyes closed. Eyes closed testing produced significant improvement in ataxia symptoms, indicating that impaired proprioception was a significant contributing factor to cerebellar ataxia in this group of patients¹².

Ayurveda

Therapy with Ayurveda, a form of traditional Indian medicine, has also been found to improve balance in patients with degenerative cerebellar ataxia¹⁰. In one study, participants received Ayurvedic oils applied to the scalp, Ayurvedic herbal supplements, massage and sauna, for between two to four weeks. The therapy was safe and well-tolerated and resulted in significant improvement in balance, particularly anterior-posterior sway, and walking ability.

Acetyl-dl-leucine

Supplementation with the amino acid acetyl-dl-leucine may offer benefits for some forms of degenerative cerebellar ataxia. In a clinical trial, published in the October 2013 issue of the Journal of Neurology, participants consumed 5 grams of acetyl-dl-leucine per day for 1 week¹¹. Researchers reported an average of 20 percent decrease in scores on an ataxia rating scale. Gait coordination and speed, speech, and hand and finger dexterity all showed improvement. No adverse side effects occurred, implying a good risk-to-benefit profile for acetyl-dl-leucine.

A Cautionary Note

If you experience cerebellar degeneration together with orthostatic hypotension, as often occurs in MSA patients, your risk of falls and injuries increases. This symptom combination can also complicate your physical therapy sessions, challenging your ability to perform exercises to improve cerebellar function due to lightheadedness and fainting brought on by neurogenic orthostatic hypotension. Discuss your needs with your physical therapist to ensure that appropriate precautions are taken during physical therapy sessions addressing cerebellar ataxia to account for potential episodes of orthostatic hypotension.

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Cerebellar Ataxia: Pharmacological Treatment Options

Currently, a lack of specific drugs for ataxia makes treatment for this condition particularly challenging²³. As a result, you may need to go through a process of trial and error to arrive at an effective drug and dosage level that adequately manages your symptoms. Reaching and maintaining your ideal weight, muscle tone and flexibility can help minimize the amount of medication you will require²³.

Gabapentin

Widely known by the trade name Neurontin, this anti-seizure drug is modeled after the neurotransmitter gamma-amino butyric acid, or GABA. Gabapentin restores levels of GABA in the brain and spinal cord, which are often depleted in cerebellar atrophy, and has been found to reduce ataxia symptoms in cerebellar degeneration¹. Gabapentin takes effect quickly, with single doses often providing significant improvement in ataxia in some people². In an animal study, gabapentin was shown to have long-lasting effects that might prevent ataxia symptoms from worsening over time³.

Gabapentin is considered highly safe and most patients experience few or no adverse effects⁴. When side effects occur they usually resolve on their own as your body becomes accustomed to the drug⁴. The most common side effects of gabapentin include uncontrolled rolling movements of the eyes²², fatigue, sleepiness, dizziness, weight gain and ankle swelling⁴. Gabapentin may also increase risk or severity of depression⁵, though some patients report that their mood improves when they take this drug⁴.

Pregabalin

A GABA-promoting drug, trade name Lyrica, pregabalin is considered to be more potent than gabapentin. Pregabalin improved scores on a rating scale of ataxia by up to 47 percent, in one study⁶. Pregabalin is considered safe with no known serious adverse effects⁷. Mild side effects such as dizziness, imbalance and fatigue may occur, as well as less common side effects, such as double vision, tremor and impaired cognition, all of which usually resolve quickly⁷.

Baclofen

This drug sensitizes GABA receptors and is primarily used as a muscle relaxer for patients with multiple sclerosis or spinal cord injury. It is also helpful in the treatment of cerebellar ataxia¹⁶. Baclofen has been shown to improve the coordination of eye movement in relation to body movement. Side effects of baclofen include slow reaction time, impaired cognition, seizure, hallucinations and irregular heartbeat¹⁷. Drowsiness, fatigue, headache insomnia nausea and excess urination can also occur with baclofen use¹⁷.

Buspirone

Also known by its trade name, BuSpar, this anti-anxiety drug is thought to boost activity of serotonin⁸

and increase activity of the neurotransmitters dopamine and norepinephrine⁹. In a 12-month clinical trial, buspirone improved certain aspects of cerebellar function, including accuracy of movement and ability to perform rapid, repetitive movements. You may need to take buspirone for one to two weeks before noticing its effects, with full effects taking up to four weeks. Buspirone is usually taken in three divided doses per day¹⁰. Side effects are few and include dizziness, drowsiness, insomnia and headache¹⁰.

Tandospirone

A serotonin-promoting drug called tandospirone improves symptoms of some types of cerebellar ataxia¹¹. Tandospirone has also been found to reduce pain, insomnia and depression¹¹. Common side effects of tandospirone include dizziness, drowsiness, insomnia, headache and gastrointestinal upset¹².

Thyrotropin-Releasing Hormone

Therapy with a pituitary gland hormone called thyrotropin-releasing hormone (TRH) may improve ataxia in some patients by improving blood flow to the cerebellum. In a study of patients with spinocerebellar ataxia, TRH significantly improved scores on an ataxia rating scale¹³. Found throughout the central nervous system, TRH is considered a neurotransmitter in certain areas, including the cerebellum, with improvement of ataxia being one of its most important effects¹⁴. However, one study found TRH to be somewhat less effective for cerebellar ataxia in MSA compared with other forms of cerebellar ataxia¹⁵.

Aminopyridine

This drug, trade name Ampyra, improves ataxia symptoms by modulating cerebellar activity so as to improve coordination of eye muscles with body movement^{18, 19}. Ampyra is used to improve walking ability in patients with degenerative nerve conditions such as multiple sclerosis²⁰. Side effects of aminopyridine include seizures and cognitive impairment²⁰.

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Dystonia: Non-Pharmacological Treatment Options

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 percent of MSA patients experience dystonia¹.

Not an early symptom of MSA, dystonias tend to manifest as the disease progresses and occur more commonly in MSA-P than MSA-C². 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 rigidity¹. 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 problems⁶. MSA patients also often experience dystonia of the muscles of the mouth and face that alters speech, resulting in high-pitched sounds¹. 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.

Physical and Occupational Therapy

Physical and occupational therapists can help in the management of dystonias by mobilizing joints to maintain range of motion and stretching muscles to minimize contracture³. 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 part³. A form of movement retraining therapy called constraint-induced therapy is used in dystonias of the hands. This approach involves taping or splinting non-dystonic fingers as a way to isolate the dystonic fingers and encourage them to function³.

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 movement⁵. Passive and active stretching techniques help mobilize the cervical spine. Additionally, use of low-level electrical stimulation on the skin surface activates the non-dystonic muscles. This causes a reflex that inhibits and relaxes the overactive, dystonic muscles⁵. 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 levels⁵. Additionally, mental health, vitality and sociability improved in the group that received physical therapy but not in the botulinum only group⁵.

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 maneuvers⁴.

posture and function, decreased pain and lowered the 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 straightens¹⁰. Though its cause is not fully understood, it is thought to be either a form of trunk muscle dystonia¹¹, unbalanced muscle rigidity or a muscular disease¹⁰. 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 position⁹.

Sensory Tricks

Touching a part of the face or head can help some patients reorient their posture⁶. The technique, known as geste antagonistique, was found, in one study, to be effective for correcting head position in half or more of patients⁷. 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 be used to give the dystonia patient a continuous stream of cues, or feedback, about the activity of those muscles⁸. 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 rotational³. Adverse effects of the surgery tend to be temporary but can include balance problems and swallowing difficulties⁶.

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Dystonia: Pharmacological Treatment Options

Botulinum Toxin

Injections of botulinum toxin, particularly in the deeper muscles of the neck, have been found helpful for cervical dystonia¹. 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 muscles³. However, dystonias of the legs may not respond as well to botulinum therapy as cervical and arm dystonias². A review of previously published studies found botulinum toxin offers significant improvement, particularly for tremor associated with dystonia, compared to drug therapies, including anticholinergic drugs, levodopa, clonazepam, β -blockers and primidone, which offer limited benefits for dystonia⁴. Side effects of botulinum toxin therapy, including dry mouth and swallowing difficulties, occur in up to 19 percent of patients³.

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 patient⁵. Side effects of levodopa can include nausea, movement disorders, sleepiness, orthostatic hypotension, and cognitive impairment⁶.

Anticholinergics

A category of drugs known as anti-cholinergics are often used to treat dystonia. These drugs work by blocking acetylcholine, the neurotransmitter that activates muscles. Examples include benztropine, biperidin, procyclidine and scopolamine⁶. 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 mouth⁶.

Tetrabenazine

This drug, which lowers dopamine levels, is primarily used to treat Huntington's chorea and has also shown some effectiveness for dystonia⁶. Side effects of tetrabenazine include sleepiness, parkinsonism, cognitive impairment, depression, orthostatic hypotension and insomnia⁷. Tetrabenazine has demonstrated effectiveness in treating cervical dystonia in Parkinson's patients⁸. Side effects may include depression, fatigue, parkinsonism and sleepiness.

Baclofen

This drug raises levels of the calming neurotransmitter GABA and is helpful for some dystonia patients⁶. Side effects may include sleepiness, nausea, cognitive impairment, dizziness and muscle weakness⁶. Baclofen use causes dependency and stopping or suddenly lowering the dose can result in seizures and delirium⁶.

Benzodiazepines

This category of drugs, including clonazepam, diazepam and lorazepam, increase GABA activity and may be helpful for some forms of dystonia⁶. However, these drugs can cause dependence, resulting in seizures and delirium if they are suddenly stopped or if the dose is lowered too quickly⁶.

Zolpidem

A GABA-enhancing drug called zolpidem, trade name Ambien, primarily used for insomnia, has also been shown to improved dystonia symptoms⁹. In one study, 37 percent of participants responded well to zolpidem⁹. In the same study, 25 percent experienced improvement with clonazepam and 19 percent 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 drowsiness¹⁰. Other potential side effects of zolpidem include headache, muscle aches, and stuffy or runny nose, constipation or diarrhea, indigestion, double vision and movement difficulties¹¹.

Muscle Relaxants

This broad range of drugs that includes some already mentioned, such as baclofen and benzodiazepines, as well as others, such as carisoprodol, cyclobenzaprine, metaxalone and methocarbamol can be helpful for managing pain of pulled or sore muscles which can occur often in dystonia⁶. Side effects of muscle relaxants are common and include drowsiness, dizziness, urinary retention and dry mouth¹². These drugs can also be addictive¹².

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Breathing Disorders: Non-Pharmacological Treatment Options

Disorders affecting breathing are a common feature of MSA and may arise from atrophy or overactivation of breathing and vocal cord muscles or a combination of the two,¹ as well as degeneration in areas of your brain that control respiration².

In one type of breathing disorder, known as stridor, a characteristic wheezing sound occurs when you breathe in. Stridor, which occurs in up to 42 percent of MSA patients⁶, 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 throat⁴. Stridor can occur throughout the day and night, or, in some instances, only during sleep³. If you are affected by stridor your respiratory rate and heart rate may increase during sleep⁷.

Stridor during sleep can also cause obstructive sleep apnea, a condition characterized by frequent, prolonged periods when breathing stops. Obstructive sleep apnea affects about 37 percent of MSA patients⁶ and episodes have been documented to occur as often as 32 times per hour⁴. 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 as low as 86 percent, compared to a normal, healthy level of 95 to 100 percent⁵.

CPAP

If you have sleep apnea or nocturnal stridor your doctor may recommend using a continuous positive air pressure (CPAP) machine. This device applies air pressure into your airways to keep them open. A pump creates the pressure, which is delivered through a hose connected to a face mask that you wear while you sleep. At first, some patients experience claustrophobic feelings from wearing the mask. As a result, it might take a few nights of using the CPAP for you 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 your face⁸. Certain 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 your face⁹.

Use of CPAP machines has been found to improve quality of sleep and increase alertness during the day in some MSA patients¹⁰. 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-term¹⁰. Studies have shown that CPAP use can eliminate or reduce stridor and obstructive sleep apnea and improve blood oxygen levels^{11,4}.

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 increasing the depth of respiration in addition to using pressure to open the airways. The 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 depth¹⁴. 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 obstruction¹⁵. In one study of MSA patients with central sleep apnea, BiPAP use eliminated stridor and improved blood oxygen levels¹⁵.

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, your 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 then 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 your lungs and the external environment, promoting better airflow, and improving breathing¹².

Learning to breathe through a tracheostomy tube may take a few days of practice. Speaking with a tracheostomy tube is also 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 damage¹³. A tracheostomy that remains in place permanently can cause long-term complications such as difficulty swallowing, blood vessel rupture and scar tissue formation¹³. Impaired blood supply to the trachea and formation of a fistula, or abnormal connection between trachea and esophagus, or food pipe, are also risks associated with tracheostomy.

Other Surgical Options

Certain structures in your throat aside from vocal cord muscles can contribute to obstructive sleep apnea. Depending on which structures might be contributing to the problem there are various surgical options to consider. If your 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, was shown, in one study, to decrease episodes of disordered breathing by more than half in 60 percent of obstructive sleep apnea patients¹⁶. 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, in some instances, become completely paralyzed, totally obstructing air flow. This constitutes a medical emergency and can happen regardless of which form of therapy you undergo. 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 throat¹⁷. To avoid respiratory failure when

breathing problems arise due to vocal cord paralysis, exercise vigilance and be prepared to respond rapidly.

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Breathing Disorders: Pharmacological Treatment Options

Botulinum Toxin

Injections of botulinum toxin can help relieve constriction of the larynx if your sleep apnea is caused or worsened by dystonia of the throat muscles¹. Botulinum injections may cause speaking and swallowing difficulties in the initial phases following injections. In one study, 51 percent of treatments resulted in moderate voice impairment and 14 percent of treatments caused participants to experience difficulty swallowing liquids². These side effects lasted for 5.7 percent of the total time between treatments and resolved as the effects of the toxin wore off. Overall, botulinum therapy produced a 30 percent gain in function.

Modafinil

If you continue to experience daytime sleepiness while using CPAP therapy at night a drug called modafinil may help. Modafinil works by increasing dopamine levels. This drug has a stimulant effect on the brain without acting like an amphetamine⁴. It promotes activity of the neurotransmitter serotonin and inhibits activity of the neurotransmitter GABA⁴ and has been shown to improve scores on a sleepiness index by an average of 40 percent³. Potential side effects of modafinil include anxiety, headache, nausea and nervousness⁵. Modafinil may also cause back pain, dry mouth, indigestion, diarrhea, dizziness, tingling or burning sensations, and swelling⁵. Side effects have been reported in up to 36 percent of participants³.

Spirolactone

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 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 percent⁵. Spironolactone is a potassium-sparing diuretic and can alter certain mineral levels. Ten percent of patients who take this drug accumulate excess potassium and 12 percent of patients develop low sodium levels⁷. Side effects include muscle paralysis and heart problems⁷. This drug may also impair kidney function, worsen Parkinson's symptoms and decrease testosterone levels⁸.

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 constriction⁹. Serotonin also influences breathing control centers in the brain⁹. Serotonin-enhancing drugs, such as **bupirone**, trade name Buspar; **fluoxetine**, trade name Prozac; and **paroxetine**, trade name Paxil may help alleviate some symptoms of sleep apnea⁹. Animal studies have shown promising results with bupirone for improving irregular breathing patterns^{10,11}. A clinical trial used a combination of the drugs fluoxetine, which activates serotonin in the brain, and **ondansetron**, 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 sleep¹², reducing episodes of apnea by 40

percent. However, use of serotonin-enhancing drugs may not alleviate daytime sleepiness¹³. Potential side effects of buspirone include restlessness, nervousness, blurred vision, sweating, dry mouth, muscle pain, difficulty sleeping, and fatigue¹⁴. Side effects of fluoxetine and paroxetine include insomnia, rash, headache, joint and muscle pain, digestive disturbance, reduced blood clotting and decreased libido¹⁵. Ondansetron has been associated with side effects such as confusion, dizziness, racing heart, fever, headache, difficulty breathing, and weakness²⁰. Less commonly, ondansetron may cause urination problems including decreased frequency, decreased volume, difficulty passing urine and painful urination²⁰.

Donepezil

Trade name Aricept, this drug decreases breakdown of the neurotransmitter acetylcholine, has been found to decrease the number of incidences of apnea and low blood oxygen per night¹³. A clinical trial of donepezil found that it significantly decreased time participants spent in a low-oxygen state, improved sleep efficiency and decreased daytime sleepiness¹⁶. Potential side effects of donepezil include nausea, diarrhea, muscle cramps, difficulty sleeping and fatigue¹⁷.

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 test¹⁸. Potential side effects of armodafinil include breathing difficulty, chest tightness, racing heart, frequent urination, itching or burning sensations, and skin rash¹⁹.

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REM Behavior Disorder: Non-Pharmacological Treatment Options

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 corroborate 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 causes actual or potential 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 percent within 5 years and 45 to 55 percent within 12 years. MSA is the most common of the alpha-synucleinopathies to be associated with RBD, with 68 to 88 percent of MSA patients affected. Antidepressant use increases risk of developing RBD by 500 percent (all facts this section ref 1).

Safety First

Safety concerns dictate that the first order of treatment for patients with RBD is to injury-proof the bedroom as much as possible¹. Remove guns, weapons and loose objects that could be used as weapons. Pad sharp corners of furniture. Place your mattress and box spring directly on the floor or place a mattress on the floor next to your bed or use bed rails around the bed to prevent or cushion 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 that was not responsive to medication². 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, sounds are processed 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.

(REM Behavior Disorder: Non-Pharmacological Treatment Options, cont'd.)

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REM Behavior Disorder: Pharmacological Treatment Options

GABA-Enhancing Drugs

Clonazepam a GABA-enhancing drug in the benzodiazepine family, reduces dream enactment in REM behavior disorder¹, or RBD. Clonazepam increases total sleep time, decreases episodes of waking up during the night and improves sleep quality⁴. However, clonazepam can worsen sleep apnea and should not be used if you have sleep apnea that is not managed. Clonazepam and other benzodiazepine drugs can also cause daytime sleepiness¹, impair gait¹, and decrease activity of serotonin, which leads to mood problems such as depression². Thirty percent of patients who take clonazepam for REM behavior disorder stop taking the drug or use a lower, possibly less effective, dose² because of these disruptive side effects. For RBD patients who are able to take clonazepam, longterm 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 night³.

One alternative to clonazepam is a drug called zopiclone, which was demonstrated to be effective for 73 percent of patients in one study and caused fewer side effects than clonazepam². Zopiclone, which is also a benzodiazepine drug, has been used for MSA patients who experience sleep apnea together with RBD and cannot take clonazepam.

Melatonin

A hormone your brain manufactures to control your body's day/night cycle, called melatonin, has been used with some success for treating RBD. Levels of the hormone, which can be obtained 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 percent⁵. Benefits were sustained during the second phase of the study, whereby 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 has also been shown to provide sufficient improvement without adverse side effects for some patients, while in others a combination of both clonazepam and melatonin is required to obtain satisfactory results¹. Though there is some concern that melatonin usage might worsen orthostatic hypotension, recent evidence points to melatonin's safety with regard to blood pressure maintenance⁶.

A drug called Ramelteon sensitizes brain cells to melatonin and has been shown effective in treatment of REM behavior disorder in MSA and Parkinson's disease⁷. 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 ineffective⁷. Potential side effects of ramelteon include dizziness, sleepiness, body aches, movement or breathing difficulties, fever and nausea⁸.

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 percent of participants⁹. A synergistic effect also occurred in this study, whereby a group that received combination therapy with pramipexole and clonazepam showed significantly greater muscle relaxation during REM sleep than 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 rhythm¹¹.

Depressants

A central nervous system depressant called sodium oxybate has been used successfully in some RBD patients who do not respond well to other medications¹². This drug is also used to reduce daytime sleepiness in patients with sleeping disorders. Side effects of sodium oxybate include hallucinations, confusion, shallow breathing, sleepwalking and waking up during the night¹³. It can also cause depression, nausea, numbness or tingling, tremor and blurred vision¹³. Because sodium oxybate takes effect within minutes, it must be taken while in bed and immediately before going to sleep¹³. Two doses per night are usually prescribed, requiring the patient to set an alarm to awaken for the second dose. Potential side effects include hallucinations, shallow breathing, sleepwalking or waking during the night. Additionally, sodium oxybate is habit-forming and can cause severe withdrawal reactions if you abruptly discontinue it¹³.

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Depression and Cognitive Impairment: Non-Pharmacological Treatment Options

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 fluency¹. 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 percent of participants showing signs of cognitive decline while a test called the Frontal Assessment Battery categorized 41 percent of participants as being cognitively impaired². Another study concluded 72 percent of participants showed mild or moderate cognitive impairment, including attention, abstract thought and delayed memory³. 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 impairment⁴ and in part from the mental and emotional stresses associated with this complex disease. MSA patients often show high scores on self-rating depression questionnaires³.

Cognitive Training

Keeping your brain active through mental exercise, such as memory games, mental arithmetic and others sharpens memory, decision-making ability and brain processing speed and can help slow age-related cognitive decline⁵. 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 periods⁶. 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^{7,8}. Animal studies have demonstrated that exercise strengthens cell-to-cell connections within the brain and improves adaptability of brain cells in Parkinson's disease⁹.

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. The 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 weeks¹⁰. rTMS is considered safe and effective, with minor side effects such as scalp discomfort¹⁰.

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Neuroprotective Diet

Though the precise cause or causes of MSA are not known at this time, food choices you make each day 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 Parkinsonism¹. In a preliminary animal study, 21 days of calorie restriction restored glutamate levels to normal¹. 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-percent calorie-reduced diet promotes healthier aging of the brain and immune system¹.

Low-Protein and Protein Re-Distribution

If your doctor has prescribed the Parkinson's drugs levodopa or carbidopa you may consider adopting a low-protein diet, which promotes more efficient use of these drugs that compete with dietary amino acids for absorption². 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 low-protein diet in one study³.

Another class of drugs used to manage Parkinson's symptoms, called monoamine oxidase inhibitors (MAOI's), prevent the breakdown of dopamine. However, MAO's 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 as well as all other aged, fermented or spoiled foods. To further reduce your 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 (all facts this paragraph ref. 4)

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 MSA⁵. Inflammation in the nervous system occurs early in Parkinsonian conditions, accelerating the degeneration of dopamine-producing cells⁹. High levels of certain types of inflammatory molecules are often present in the early stages of MSA¹¹. 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 you manage some of your symptoms and slow the disease process.

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-life⁶ for similar foods cooked with healthy vegetable oils. Prepare fresh foods at home as much as possible using olive and canola oils. 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-3's, onto hot or cold cereal and drizzle flax seed 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 day⁶. 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 micro-nutrients, such as quercetin and flavonoids⁷. 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 benefits⁸.

High Anti-Oxidant 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 products¹⁰. Sulphoraphane, a compound in broccoli, cauliflower, cabbage and other cruciferous vegetables increases activity of cellular antioxidant defense mechanisms. Curcumin, the active ingredient in turmeric, is also being studied for mitochondrial and neuroprotective benefits¹⁰.

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Constipation: Non-Pharmacological Treatment Options

Autonomic dysfunction may slow the normal, rhythmic movement of your 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.

Exercise

Physical exercise helps activate peristalsis, improves stomach emptying and is protective against colon cancer, which is more prevalent in people who experience chronic constipation³. Stay as active as you can 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, use decaffeinated coffees and teas. Alternatively, you can offset their diuretic effects by consuming extra water.

Fiber

A high-fiber diet is also 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 can 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 to be the most effective remedy for chronic constipation in older adults, in a research review⁴. 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. If you take psyllium or other bulk-forming laxatives it is important to consume sufficient fluids; otherwise the soluble fiber will form a hard mass, which can cause intestinal blockage. If you have swallowing difficulty you may find it 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 fenugreek⁵.

Calcium Polycarbophil, brand name FiberCon, a synthetic, bulk-forming laxative, has been found to be nearly as effective as psyllium⁴. Calcium polycarbophil significantly decreases inflammation in the

lining of the colon caused by chronic constipation⁶ and has been shown to shorten transit time through the colon and increase frequency of bowel movements in MSA patients⁷. Potential minor side effects of calcium polycarbophil include stomach pain, bloating and gas⁸. Serious, though less common side effects include vomiting, difficulty swallowing, chest pain and rectal bleeding⁸. If these occur, you should seek medical attention.

Stool Softeners

Docusate sodium and docusate calcium coat the surface of the stool to soften it and allow for easier passage⁹. However, they do not promote peristalsis, the muscular intestinal action that moves contents through the colon, so are often combined with stimulant or bulking laxatives⁹. Docusate is generally safe and well-tolerated¹⁰. Reported side effects include intestinal cramping, skin rash, and depletion of magnesium¹⁰.

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 tract¹¹. Polyethylene glycol tends to be more effective than lactulose for chronic constipation. These can occasionally cause electrolyte imbalance that can impact heart and kidney function¹¹. Less serious side effects include abdominal cramping, nausea, bloating and flatulence¹¹.

Stimulants

Anthraquinone, the active ingredient in the herbs senna, aloe and cascara sagrada, 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 FDA has banned their use in over-the-counter laxatives (all facts ref 12).

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Constipation: Pharmacological Treatment Options

Serotonin-Promoting Drugs

Tegaserod, a newer generation therapy, works by activating the neurotransmitter serotonin. Usually thought of in conjunction with brain function, 95 percent of the serotonin in your body is actually located in your digestive tract where it controls nerves, muscles, endocrine function and blood supply². Tegaserod has been shown to increase bowel movement frequency and decrease bloating and discomfort². It may cause diarrhea for a couple of days, but this usually resolves as your body becomes accustomed to it². Other reported side effects include headache, sore throat and abdominal pain. However, in one trial, all side effects except diarrhea were more common in the placebo group than in the groups that received the drug². Tegaserod is approved for use in adults younger than 65 years. A 13-month study found it to be safe for long-term use².

Other serotonin-promoting drugs that have been found helpful in patients with chronic constipation include mosapride citrate, brand name Mosapride, and prucalopride, brand name Resolor³. 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 constipation⁴. Mosapride citrate has been found helpful in patients with chronic constipation due to irritable bowel syndrome (IBS)^{5,6} and causes few or no side effects¹.

Fatty Acids

Lubiprostone, a fatty acid compound, is the newest drug to receive FDA approval for treating chronic constipation². 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 you stop taking it². 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 distension, abdominal pain and gassiness². In a review of laxatives for older adults with chronic constipation, lubiprostone was 39 percent more effective than placebo⁷.

Pain Management

Gabapentin and pregabalin, drugs that promote activity of the calming neurotransmitter GABA, have been used to help reduce pain and hypersensitivity of the intestinal tract².

References

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