

GENERAL INFORMATION BROCHURE ON ORTHOSTATIC INTOLERANCE AND ITS TREATMENT

Chronic Fatigue Clinic
Johns Hopkins Children's Center
June 2010

Orthostatic intolerance is an umbrella term for several conditions in which symptoms are made worse by upright posture and improve with recumbency. This document provides further information about neurally mediated hypotension (NMH) and postural tachycardia syndrome (POTS), two common forms of chronic orthostatic intolerance. Hypotension is the medical term for low blood pressure (BP), and tachycardia is the medical term for an increased heart rate (HR).

What are NMH and POTS?

Neurally mediated hypotension refers to a drop in blood pressure that occurs after being upright. We define NMH by a drop in systolic BP of 25 mm Hg (compared to the BP measured when the person is lying flat) during standing or upright tilt table testing. Although NMH may be slightly more common in people with a low resting blood pressure, most people who develop NMH during standing have a normal resting blood pressure. NMH is an abnormality in the *regulation* of blood pressure during upright posture. It occurs if too little blood circulates back to the heart when people are upright, a situation that can trigger an abnormal reflex interaction between the heart and the brain that results in a lowering of blood pressure. NMH is sometimes known by the following names: the fainting reflex, delayed orthostatic hypotension, neurocardiogenic syncope, vasodepressor syncope, vaso-vagal syncope. Syncope is the medical term for fainting.

Postural tachycardia syndrome refers to an exaggerated increase in heart rate with standing. A healthy individual usually has a slight increase in heart rate—by about 10-15 beats per minute—within the first 10 minutes of standing. POTS is considered present if the heart rate increases by 30 beats per minute, or if it reaches 120 beats per minute or higher over the first 10 minutes of standing, accompanied by orthostatic symptoms. POTS is an abnormality in the *regulation* of heart rate; the heart itself is usually normal. Some patients with POTS in the first 10 minutes of upright standing or tilt testing will go on to develop NMH if the test is continued; the two conditions often are found together, and they are not mutually exclusive diagnoses.

How does upright posture lead to these problems?

When a healthy individual stands up, gravity causes about 10-15% of his or her blood to settle in the abdomen, legs, and arms. This pooling of blood means that less blood reaches the brain, the result of which can be a feeling of lightheadedness, seeing stars, darkening of vision, or even fainting. For most of us, this lightheaded feeling is infrequent when we stand up because the leg muscles help pump blood back up to the heart, and because the body turns on a series of rapid reflex responses. To make up for the lower amount of blood returning to the heart immediately after standing, the body releases norepinephrine and epinephrine (also known as adrenaline). These substances typically cause the heart to beat a little faster and with more force (a familiar feeling after we exercise or are frightened), and norepinephrine causes the blood vessels to tighten or constrict. The end result is more blood returning to the heart and brain. Most of the time, we are unaware of these reflex changes in blood flow when we stand up.

When people with either NMH or POTS are upright, they appear to pool a larger amount of blood in vessels below the heart. Compared to healthy individuals, for the person with NMH or POTS, the longer they remain upright, the greater the proportion of their blood that settles in their abdomen and limbs. The body responds by releasing more norepinephrine or epinephrine, in an attempt to cause more constriction of the blood vessels. For a variety of reasons, not all of which are well understood, the blood vessels do not seem to respond normally to these substances, and the vessels either do not constrict efficiently or they dilate. Because the heart remains able to respond to the norepinephrine and epinephrine, the heart rate often increases.

In those with POTS, the main result of excessive pooling of blood during upright posture is an exaggerated rise in heart rate. In those with NMH, the main result is a reflex lowering of blood pressure. Some of this is caused by a “miscommunication” between the heart and the brain, both of which usually are structurally normal. Just when the heart needs to beat faster to pump blood to the brain and prevent fainting, the brain sends out the message that the heart rate should be slowed down, and the blood vessels should dilate further. These actions take even more blood away from where it is needed in the central part of the circulation. At this time, it is not entirely clear why some people develop NMH and some develop POTS, although it may relate in part to the balance of epinephrine and norepinephrine release in the system.

Which symptoms can be caused by NMH or POTS?

Any time the brain is getting too little blood flow, the usual result is a lightheaded or spacey feeling. Some people describe this as a “head rush.” Recurrent lightheadedness is a common symptom of both NMH and POTS. If lightheadedness is severe, individuals may have dimming of their vision, may hear sounds as though they were far away, and may have nausea or vomiting. They may faint because not enough blood is getting to the brain. Fainting is helpful, in that it restores a person to the flat position, removing the effect of gravity on blood pooling in the limbs, and allowing more blood to return to the heart. Following the episodes of lightheadedness or fainting, most people feel tired for several hours (sometimes more than a day) and their

thinking can be somewhat foggy. Some patients with NMH or POTS experience prolonged fatigue after a modest amount of physical activity, or after sustaining quiet activity like sitting at a desk. This fatigue after exertion or sustained activity can also last 24-72 hours, and can interfere with many daily activities.

While fainting has been considered a classic symptom of NMH, we have found that many persons who develop NMH during tilt table testing do not faint in day-to-day life. Chronic fatigue, muscle aches (or myalgias), headaches, nausea, and mental confusion can be prominent symptoms of NMH in these individuals. The mental confusion takes the form of difficulty concentrating, staying on task, paying attention, remembering, or finding the right words. Some describe being in a “mental fog.” Some develop worse fatigue after mentally demanding activities, such as reading and concentrating. This may occur because the blood vessels of the limbs dilate rather than constrict in response to mental tasks, allowing more blood to pool.

In persons with POTS, a fast heart rate is a defining feature, and awareness of vigorous or skipped heart beats (palpitations) is common. In addition, patients can experience lightheadedness, intolerance of exercise, fatigue, visual blurring, weakness, imbalance, headaches, shakiness, clamminess, anxiety, shortness of breath, and the same type of mental foggy that those with NMH describe.

It has now been established that there is a substantial overlap between syndromes of orthostatic intolerance on the one hand, and either chronic fatigue syndrome (CFS) or fibromyalgia (FM) on the other. It needs to be emphasized that not all those with NMH or POTS have CFS or FM, and not all with CFS or FM have NMH or POTS.

When do NMH and POTS lead to symptoms?

Symptoms of NMH and POTS usually are triggered in the following settings:

- * with quiet upright posture (such as standing in line, standing in a shower, or even sitting at a desk for long periods),
- * after being in a warm environment (such as in hot summer weather, a hot crowded room, a hot shower or bath),
- * immediately after exercise,
- * after emotionally stressful events (seeing blood or gory scenes, being scared or anxious).
- * in some people, after eating, when blood flow shifts to the intestines during digestion.
- * if fluid and salt intake are inadequate

It is thought that we all would develop NMH provided the environmental conditions were sufficiently severe: for example, if we did not take in enough fluids or salt, or were subjected to extremely prolonged periods of upright posture or to very warm environments. The reflex response that results in lowered blood pressure simply occurs at an earlier point in some individuals. Each person’s susceptibility is affected by a number of factors, including genetics,

diet, psychological make-up, and the presence of other medical disorders including infection, inflammation, or allergy. Some people may develop NMH or POTS during tilt testing, but not be affected much in regular daily life. A person is treated for NMH or POTS when there is enough early triggering of symptoms to interfere with normal activity.

How are NMH and POTS diagnosed?

NMH and POTS cannot be detected with routine, resting blood pressure or heart rate screening. The diagnoses can be made with a prolonged standing test or a tilt table test. Although a 10-minute test is all that is needed to diagnose POTS, this is too brief for diagnosing NMH, which usually requires at least a 45-minute period of upright posture. Many hospitals and academic centers throughout the world perform tilt table testing. It allows careful measurement of the heart rate and blood pressure responses to the head-up position, usually at a 70-degree angle, in an almost standing position. The usual reason for performing a tilt table test in the past had been for the evaluation of recurrent fainting. Many people with NMH develop adaptations to keep from fainting, such as crossing their legs, fidgeting, or sitting or lying down when they get lightheaded or tired. However, during the tilt table test they must remain still, and they cannot call upon these natural defenses. As a result, fainting can occur for the first time during the tilt table test. Increased fatigue and malaise often occur for a few days after the test is performed, although our experience has suggested that these symptoms can be minimized if the individual is treated with intravenous saline solutions immediately after completion of the tilt test.

What causes NMH or POTS?

The answer to this question isn't well understood at present. We suspect NMH and POTS have genetic origins in many people, because it is not uncommon for us to find several affected individuals with some form of orthostatic intolerance in the same family. No gene for NMH has been identified, but one rare genetic cause has been found for POTS. One trait seen with increased frequency in those with CFS and orthostatic intolerance is excessive joint mobility; some patients with joint hypermobility have a connective tissue disorder known as Ehlers-Danlos syndrome. The reasons for the association between NMH and POTS and joint hypermobility disorders are not yet clear, but these are examples of genetic influences on NMH and POTS.

A number of persons with NMH or POTS report that their symptoms began after an infection or physical trauma (such as an apparent viral illness, sinus infection, mononucleosis, Lyme disease, a car accident, or surgery). Other environmental factors may also play a role, but more research is needed before we will know what actually causes either condition.

Some investigators have noted an overlap in the symptoms of fatigue and conditions in which there is too little room for the spinal cord in the neck or as it emerges from the skull (conditions known as cervical spine stenosis or Chiari malformation). It needs to be emphasized that these conditions do not explain the presence of POTS or NMH in the vast majority of patients, and further studies are needed regarding the best methods to diagnose and treat these abnormalities.

One of the most common and treatable problems identified in those with NMH and POTS is a low salt (sodium) intake in the diet. Salt helps us retain fluid in the blood vessels, and helps maintain a healthy blood pressure. Salt has received bad press in the last couple of decades because a high salt diet in some individuals with high or high-normal blood pressure can lead to further increases in blood pressure, and thereby contribute to heart disease and stroke. This has led to general health recommendations to “cut down on salt.” As we are finding, this general recommendation isn’t right for all people.

In adults, an average blood pressure is 120/70. An adult’s systolic blood pressure [the top number] is considered low if it is below 100, and it is considered elevated if it is above 140. An adult’s diastolic blood pressure [the bottom number] is considered high if it is over 90. Normal values for BP in children and adolescents vary by age and weight. Individuals can have NMH at a wide range of resting blood pressures. It may be slightly more common in those whose systolic BP is in the 90-110 range. For individuals with NMH, a low salt intake may be unhealthy; reducing sodium intake may move them from feeling good to developing the symptoms of fatigue and lightheadedness described earlier. In experimental work earlier this century, severe short-term salt depletion led to fatigue and mental dulling in the adult research participants.

How are NMH and POTS treated?

Treatment of these conditions is often quite challenging. Because patients have a different mix of underlying contributors to their orthostatic intolerance, therapy has to be tailored to the individual, and usually requires persistence and a willingness to try multiple methods. The approach we use has been based on the available evidence from formal studies and from our experiences treating large numbers of individuals. We use a stepped approach. Step 1 focuses on non-pharmacologic treatments, Step 2 involves use of a single medication, and Step 3 involves rational and judicious use of more than one medication.

Step 1: Non-pharmacological treatments:

- a. Avoid prolonged sitting, quiet standing, warm environments, and vasodilating medications.

Where practical, avoid circumstances that commonly bring on symptoms. For example, shop at non-peak hours to avoid long lines. Take shorter showers and baths and aim for a cooler water temperature. Avoid saunas, hot tubs, and lying on a hot beach. Avoid standing still for prolonged periods in hot environments, and on very hot days. Flex your leg muscles and shift

your weight when you are standing still. You may also want to avoid alcohol because it causes loss of fluids and often leads to dilation of the veins, which can “steal” blood away from the central circulation. Many with NMH are quite intolerant of alcohol. High carbohydrate meals have been shown to reduce blood vessel constriction in response to upright stress, so a lower carbohydrate intake and frequent small meals may help. Caffeine intake (including caffeine in soft drinks) affects some people with NMH or POTS positively and some in an adverse way, so examine whether caffeine is helping you or making symptoms worse.

An important aspect of treating NMH or POTS is to review your current medications and nutritional supplements with your doctor or health care provider to ensure that these do not have the potential to make your symptoms worse. Narcotic medications (like codeine, morphine, oxycodone) and phenothiazine anti-emetics (like Phenergan or Compazine) can lead to more blood pooling, and niacin can cause vasodilation. Many patients develop hypotension when treated with high doses of nortriptyline, amitriptyline, or similar tricyclic antidepressants; low doses of these medications often are tolerated.

b. Use postural maneuvers and pressure garments.

Certain postures and physical maneuvers can help reduce NMH and POTS symptoms when people are upright, mainly by using contraction of the leg muscles to pump blood back to the heart and by compressing the abdomen to reduce the amount of blood that pools in the intestinal circulation. These small changes may be important, as even a small increase in blood return to the heart can help maintain an adequate blood flow to the brain. Many patients have adopted these postures without knowing why. The helpful maneuvers include:

- * standing with one's legs crossed
- * squatting
- * standing with one leg on a chair
- * bending forward from the waist (such as leaning over a shopping cart)
- * sitting in the knee-chest position
- * sitting in a low chair
- * leaning forward with hands on the knees when sitting.

Some of these postures are less conspicuous than others. Sitting in a low chair (such as a camping stool) is helpful because it causes the legs to be brought up toward the abdomen, and probably reduces the amount of blood pooling in the intestinal circulation. For similar reasons, avoid sitting in a high chair with the legs dangling freely, as there is no resistance to blood pooling unless the muscles are actively contracting. One young woman found she could sit longer without symptoms if she put her feet on a low foot rest (this probably required more leg muscle contraction than regular sitting, and may have also compressed the abdomen better). Some patients get worse if they adopt these postures, so they may not be right for everyone. Another technique has been shown to help reduce the frequency of

fainting, and involves 2 minutes of maximum contraction of the arms (gripping one hand with the other and pushing the arms away) at the start of lightheadedness.

Another time-honored recommendation is to elevate the head of the bed slightly by 10-15°, so that the head is higher than the feet, a position that appears to help the body retain fluid at night rather than lose fluid into the urine.

In the research setting, several studies have shown that if blood vessels can be compressed from the outside (using tight compression garments or military anti-shock trousers), the abnormal heart rate and BP changes of NMH or POTS can be reduced or eliminated. In day-to-day life, waist-high support hose can prevent some of the excessive pooling of blood in the legs (knee-high support socks help somewhat), as can garments that increase abdominal compression (these work by preventing excessive amounts of blood pooling in the intestinal circulation), such as abdominal binders and abdominal corsets.

c. Treat contributing medical conditions.

Attention to other medical conditions is crucial to ensuring that the NMH or POTS treatments are as effective as they can be. In particular, preventing activation of even mild asthma and allergies has been important in keeping our patients from developing a worsening of symptoms. In patients with asthma, we usually try to reduce reliance on albuterol and other beta-agonist inhalers, as these medications can mimic the effect of too much epinephrine, and can aggravate NMH in particular. Endometriosis and other painful conditions may aggravate symptoms, and ovarian vein varices (pelvic congestion syndrome) in women with pelvic pain are associated with fatigue and worse orthostatic intolerance. Sinusitis, anxiety disorders, depression, migraine headaches, and infections of any sort are examples of other conditions that need appropriate medical attention when present.

Allergies or delayed hypersensitivities to food proteins (most commonly cow's milk protein) can co-exist with orthostatic intolerance, and unless they are addressed they can obscure any improvements that might otherwise come with medications and postural changes. Dr. Kevin Kelly has identified the following symptoms that should prompt us to think further about the possibility of a food allergy or hypersensitivity: upper abdominal pain, gastroesophageal reflux, and appetite disturbance (filling up too quickly, picky appetite), sometimes with recurrent mouth ulcers, headaches, sinusitis, and either constipation or diarrhea. If hypersensitivity to a food protein is playing a role, substantial improvements can result from strict exclusion of offending foods. We would emphasize that this dietary treatment is not part of the standard treatment of NMH and POTS in our clinic, and is only considered on the basis of the specific symptoms mentioned above. Given the potential dangers of unsupervised diets, be sure to discuss these issues with your doctor or health care provider.

d. Increase salt and fluid intake.

NMH and POTS are most often treated with a combination of increased salt and water

intake. The increased salt and water help ensure that the blood vessels are filled better, and that the heart receives an adequate amount of blood even during upright posture. Drinking a glass of water before venturing out often helps people tolerate the activity. We recommend at least 2 liters of fluid per day. Our patients who drink fluids regularly throughout the day seem to do better than those who don't take this task seriously. Keep in mind that prolonged periods of sleeping (more than 12 hours) may interfere with the ability to keep up with fluid needs. We recommend drinking fluids every 2 hours throughout the day. As a result, it is important to have easy access to fluids at work or at school.

For those who have been on a low salt intake we recommend an increase in the amount of salt they add to their food. The Appendix to this document contains a list of high salt foods. For some mildly affected individuals, an increased intake of salt and fluids may be all that is needed. Most of those with more severe symptoms require one of several medications in addition to the increased salt and fluid intake. The increased salt and fluid intake should be continued regardless of which of these medications is added.

e. Physical therapy and exercise

Exercise is important in regaining the effects that fitness brings in counteracting NMH or POTS. Because exercise can make NMH or POTS symptoms worse in the period before effective treatment has been found, it must be done carefully at first. When you and your doctor feel you are ready, begin a regular regimen of exercise, finding something that does not make you lightheaded and doing it for brief periods at first, increasing gradually. For example, one adolescent who had been ill for several years began functioning better once two of the NMH medications were working for her. She began exercising on a treadmill, but this made her lightheaded, so she switched to a reclining exercise bike. Although she started with only 2 minutes a day, she increased this in small increments up to 30 minutes 3 times a week after about three months. Walking, water jogging (the water acts as a compressing force to counteract blood pooling in the limbs), stretching, and Tai Chi or yoga may be gentle ways to ease back into exercise. Remember to warm up slowly before, and cool down gradually after exercise. If you plan to exercise outdoors, remember that extreme heat will worsen NMH or POTS.

A group of our physical therapist colleagues in Baltimore, led by Rick Violand, PT, have helped us to identify a relatively high frequency of postural asymmetries and areas of adverse mechanical tension in the nervous system as contributors to pain, lightheadedness, and fatigue in many of our patients with orthostatic intolerance. These movement restrictions can be present even in those with generally increased joint flexibility. The presence of mechanical barriers to normal range of movement throughout the body has helped explain why some patients were finding that exercise led to substantial worsening of symptoms. Among those who have the worst of these postural restrictions, several weeks of gentle manual physical therapy often prepares them to tolerate the mild aerobic exercise that would have caused a flare-up beforehand. We think careful attention must be paid to postural

asymmetries and restrictions in mobility during the physical examination, and the diagnostic expertise of a physical therapist may be essential to identifying problems. Manual techniques that our colleagues employ include gentle neural mobilization (or neural tension work), myofascial release, and cranio-sacral therapy. Building up leg strength once exercise is tolerated using resistance exercises has been found to be helpful in combating orthostatic symptoms.

Steps 2 and 3:

For those with more frequent or more severe symptoms, the physical maneuvers, dietary changes, and physical therapy of Step 1 may need to be supplemented by medications. Most of the drugs in common use for NMH and POTS help to improve the ability of the vessels to constrict and return blood to the heart when we stand, increase the amount of salt and fluid the kidney returns to the circulation, or alter the release or response to norepinephrine or epinephrine.

While many of the medications listed below have been used by physicians for years to treat NMH or POTS, few have been studied formally in those with POTS, NMH, or chronic fatigue syndrome. Some have been tested in patients who have fainted one or more times, but are otherwise healthy; some have been tested in those with ongoing symptoms due to POTS, and some have been tested in NMH patients who were diagnosed with chronic fatigue syndrome. This handout is based upon available research and our experience with NMH and POTS patients, most of whom came to see us because of chronic fatigue syndrome. The treatments listed require persistence, commitment, and the willingness to try several possible drugs and combinations over an extended period of time. Because there is a risk of serious side effects with some of the drugs (such as elevated blood pressure, elevated sodium levels, lowered potassium levels, or depression) careful monitoring is required. The following list illustrates medications that have been reported to help improve symptoms or tilt table responses in patients with NMH or POTS:

Medications that increase blood volume:

Fludrocortisone (Florinef)
Oral contraceptive pills
Clonidine
Vasopressin

Medications that interfere with the release of or response to epinephrine and norepinephrine:

Beta-blockers (e.g., atenolol, propranolol)
Disopyramide (Norpace)
Angiotensin converting enzyme inhibitors/angiotensin receptor blockers

Medications that improve vasoconstriction:

Stimulants: (e.g., methylphenidate [Ritalin] or dextroamphetamine [Dexedrine])
Midodrine (Proamatine)

Modafanil (Provigil)

Pseudoephedrine (Sudafed)

Selective serotonin reuptake inhibitors (examples include fluoxetine [Prozac], sertraline [Zoloft], and escitalopram [Lexapro]) or related medications like Effexor or Cymbalta. These medications may also affect the central nervous system reflex pathways in NMH as well.

Miscellaneous medications:

Pyridostigmine bromide

Some of the medications no doubt work in more than one way. For example, fludrocortisone improves the ability of the blood vessel to constrict in addition to expanding blood volume. Your health care provider should work with you to determine the best possible combination for your personal situation.

Does treatment cure the problem?

It needs to be stressed that, when successful, the medications for NMH and POTS usually do not cure the problem. Rather, they help control symptoms and allow a greater level of physical activity. When medications are stopped or when salt intake is reduced, symptoms frequently reappear. Many with NMH or POTS have symptoms resurface or worsen at busy or stressful times (making an oral presentation, having company over, rushing on a hot day and forgetting to drink), when they have an infection, or when their allergies are more active. The intravenous infusion of saline solutions has been shown in experimental settings to help reduce symptoms, and the judicious use of IV fluids periodically has a role.

Even after successful treatment, many women with NMH and POTS describe a worsening of symptoms in the days around the start of a menstrual period. Some women choose to take birth control pills on a 28 day cycle, or continuously (to have a period about every 3 months), in addition to their NMH or POTS medications. This is done to avoid symptoms related to hormone changes, and should be discussed with your health care provider.

The question of what happens over the long term has not been adequately studied, and the optimal duration of medical treatment is still being worked out. Unfortunately, despite appropriate doses of the available medications for neurally mediated hypotension, some people with NMH or POTS do not experience an improvement in symptoms, and some are intolerant of the medications. This emphasizes the need for more research on this problem. Many adult women who have orthostatic intolerance describe an improvement in symptoms when they have been pregnant, and often describe pregnancy as the time when they felt “the best ever.” The improvement may be due to an expansion of blood volume that occurs naturally with pregnancy.

Finally, we suggest you take an active role in your care. If you have POTS, it might be helpful to learn how to take your pulse. If you have NMH, you may want to purchase a home blood pressure monitor – we suggest the kind with a cuff that goes around your upper arm, not

around your wrist or on your finger. Heart rate and BP do not have to be taken routinely each day, but having this information during flare-ups of symptoms may provide helpful insights. Being able to monitor your blood pressure at home or take your own pulse won't replace visits to your physician or health care provider, but may make those visits more productive, as this information may reflect how you are responding to a high salt/high fluid diet or to medications.

Peter C. Rowe, MD

Sunshine Natural Wellbeing Foundation Professor of Chronic Fatigue and Related Disorders.

Department of Pediatrics, Johns Hopkins University School of Medicine.

Director, Chronic Fatigue Clinic, Johns Hopkins Children's Center.

Opportunities for philanthropy:

The CFS Clinic at the Johns Hopkins Children's Center has been able to remain in operation over the past 15 years, providing direct care for over one thousand individuals with CFS, and indirectly helping others by consulting with other physicians in the region and around the world. This has only been possible through the generosity of many individuals, families, and foundations. Our goal is to continue to expand funding to provide more staff for both clinical and research efforts. Those wishing to contribute to this effort are asked to contact:

Jennifer Balzano

Associate Director of Development

Johns Hopkins Children's Center

One Charles Center

100 N. Charles St., Suite 200

Baltimore, MD 21201

410-516-4513

www.hopkinschildrens.org

SUGGESTIONS FOR A HIGH SODIUM DIET

An adult requires between 2000 and 3000 milligrams (mg) of sodium to maintain health. Although health advice in the last two decades has suggested that a low salt intake helps prevent heart disease and stroke, many individuals with orthostatic intolerance cannot tolerate this low salt diet. We believe that individuals with neurally mediated hypotension or postural tachycardia syndrome need to take in much higher amounts of salt.

The exact amount needed is different for each individual, and is often affected by your taste for salty foods, but it is difficult to take too much, provided that you have access to lots of fluids if you become thirsty. A few individuals have been unable to tolerate an increase in sodium intake without developing increased weight gain, headache, or agitation.

Table salt is also an excellent source of sodium, as it has 2300 mg of sodium per teaspoon. Salt tablets are a way of getting enough sodium without dramatically changing the taste of your foods. If you decide to increase your sodium intake with salt tablets, we suggest that you start slowly, and work gradually up to 900-1000 mg three times a day. Some patients tolerate even higher doses. The amount tolerated varies from person to person. By stepping up your dose slowly, you can determine how much is optimal for you within this range. Remember that if you change your diet to increase sodium intake from your food, you may not need as many salt tablets. Some of our patients report better tolerance of a buffered salt tablet (the commercially available brand, Thermotabs, contains 450 mg sodium chloride and 30 mg potassium chloride). Salt tablets are available without a prescription.

As for fluid intake, be sure to drink at least 2 liters of fluid a day. Water is fine, but some prefer sports drinks (which have the advantage of a higher sodium content), and other commercially available rehydration fluids contain substantially more sodium than sports drinks. The following are high salt foods to help with your needs:

Breads and cereals:

Mg sodium

Noodles, potatoes, rice from instant mixes	500
Wheaties (1 cup)	400
Waffles (one)	355
All Bran (½ cup)	285
Cheerios (1 cup)	260
Rice Krispies (1 cup)	260
Saltine crackers (6)	200

Dairy Products:**Mg sodium**

Parmesan cheese (1 oz.)	450
Processed cheese and cheese spreads (1 oz.)	320
Cottage cheese (½ cup)	230

Fruits and vegetables:

Dill pickle (1)	1430
Tomato juice (8 oz)	800
Sweet pickle (1)	570
Frozen vegetables with special sauces (½ cup)	375
Canned tomato sauce and puree (¼ cup)	370
Canned vegetables (½ cup)	245

Meat, poultry, fish:

Enchilada	1300
TV dinner (1)	1200
Sweet-n-sour pork (1 serving)	1100
Lasagna (1 serving)	1000
Soup, canned (1 cup)	895
Fish-n-chips (1 serving)	750
Hamburger (1)	690
Hot dog (1)	550
Tuna, canned (½ cup)	535
Corn beef (1 oz)	530
Fried chicken (1 serving)	530
Pizza, cheese (1 slice)	500
Pork-n-beans, chili (1 cup)	460
Luncheon meat (1 slice)	300
Bacon (4 slices)	280

Snacks, condiments:

Pretzel Stix, 1 tray (28 g)	1460
Soysauce (1 tbsp)	870
Olives, green (4)	600
Salted nuts (½ cup)	420
Olives, ripe (4)	400
Fruit pie (1/8 pie serving)	355

INFORMATION ON MEDICATIONS USED FOR TREATING NMH OR POTS

Very few of the medications listed below have been tested in formal clinical trials in those with CFS. Some drugs have been tested in clinical trials in those who faint but are otherwise healthy. Some drugs are given in combination with others, but rigorous studies of combination therapy have not yet been done. The information presented is based on the available research, and the clinical experience of our group and others who study orthostatic intolerance.

1. FLUDROCORTISONE

Brand name: Florinef

Type of drug: a mineralocorticoid steroid

Indication: NMH or POTS

Action: Florinef acts in the kidney to help the kidney retain sodium that would otherwise be lost in the urine, and it may also help blood vessels constrict more readily in response to epinephrine and norepinephrine. It helps the body avidly retain the salt you eat. It does so at the expense of losing potassium into the urine, so it is important to take in adequate amounts of potassium each day. We recommend potassium supplements when people start on Florinef, regardless of the serum potassium level, and especially if individuals remain on the drug for several months. A sustained release potassium preparation (containing 8-20 mEq) given once daily has been well tolerated by our patients.

In our clinical trial of Florinef in adult chronic fatigue syndrome patients with NMH, the drug was not effective when given by itself. Several studies suggest the drug is helpful in treating NMH and POTS when given in combination with an increased intake of salt and other medications (for example, with a low dose of a beta blocker), but no rigorous studies of combination therapy have been conducted, and no studies in adolescents have been performed.

Common confusions: Cortisone and fludrocortisone differ. At the doses used in clinical practice, Florinef has minimal anti-inflammatory properties, in contrast to cortisone or prednisone, and it has no effect on blood sugar as cortisone does. Florinef is not a muscle building (anabolic) steroid. NMH or POTS patients taking Florinef should be on a high salt diet.

Common side effects: To reduce the chance of Florinef causing an elevated blood sodium level, make sure to drink lots of fluids while taking Florinef. Some individuals complain of headache after Florinef and some develop worse CFS symptoms (more lightheadedness or fatigue), abdominal discomfort of a new type or severity, new chest discomfort, or tearfulness and depression. Depression occurs in fewer than 1 in 20 patients, but patients need to be aware of this when they start on the drug, and to know to stop Florinef if such depressed mood occurs.

Some have found that minor side effects will disappear after a couple of weeks, and it is

worth persevering with the medication provided that the side effects are minor. Some develop worse acne on Florinef. The tablet has a tiny amount of lactose in it, and may cause discomfort to those who are extremely allergic to milk protein. Special pharmacies can compound the drug without lactose or milk protein (e.g, Abrams Royal Pharmacy, 8220 Abrams Rd., Dallas, TX 75231; Tel: 214-349-8000; Fax: 214-341-7966).

With high doses, or even low doses over a long period of time, Florinef can lead to an elevation of blood pressure (BP), especially when other medications like oral contraceptives are added to the regimen. For this reason, we recommend that BP be monitored carefully, especially in the weeks after starting on the drug, and monthly once a stable dose is achieved.

Suggested doses for patients with NMH or POTS: Because the optimal dose can vary considerably, we suggest that those who use Florinef begin with a low dose and increase it gradually. We recommend beginning with a week of increasing salt and fluid before starting on Florinef to ensure better tolerance of the drug. Once you are ready to start, begin with ½ tablet per day for a week, then increase to a full 0.1 mg tablet daily. A slower dosage advancement is to start with 1/4 tablet per day (0.025 mg). If the 1/4 tablet dose is tolerated for 4-7 days, increase to ½ tablet for 4-7 days, then to 3/4 tablet or a full 0.1 mg tablet. By stepping up the dose gradually, you can better determine the right dose (some patients may only need ½ tablet or ¾ tablet). Some patients report that splitting the dose (half in the morning and half with the evening meal) provides a more even effect, but occasionally people have to return to a once a day morning dose because the Florinef taken later in the day causes them to develop insomnia.

Each patient's tolerance of the drug and response to it is somewhat different, so we recommend regular visits while the doses are being adjusted. If there is no improvement, or more bothersome side effects appear (worse headaches, substantial weight gain, and certainly depressed mood) we recommend stopping the medication. If people continue to experience some benefit from week to week at a particular dose, it makes sense to continue on that dose. If there are no adverse effects on a dose of 0.1 mg per day, but no impressive therapeutic benefits have occurred after about a month, we will try increases to a maximum of 0.15 or 0.2 mg (1 ½ - 2 tablets) per day. Whether further increases would be beneficial is unclear. If unsure about whether the drug is having a beneficial effect, it can be stopped for a few days to see if symptoms worsen. When Florinef is helping, but only incompletely, we usually continue this medication and then add other classes of medication to it.

Comments: It is important to be sure that you are taking an adequate amount of fluid. We recommend checking the serum electrolytes periodically, but the optimal frequency for doing so is not established. Because licorice root can have the same effect on blood pressure as Florinef, combining these two medications should be avoided. If BP increases over time, a reduction in the Florinef dose may be indicated.

Use in pregnancy: consult with your health care provider.

2. ATENOLOL

Brand names: Tenormin (other similar medications like propranolol or metoprolol may be as effective, but the greatest experience has been with atenolol, and we will focus on atenolol here).

Type of drug: a beta-blocker

Indications: NMH and POTS

Action: Atenolol blocks the effects of adrenaline (epinephrine), and acts both to decrease the heart rate and to prevent the forceful heart contractions that may help trigger NMH.

Common side effects: Some individuals complain of headaches or fatigue after atenolol, and others have worse lightheadedness or worse symptoms in general. If these problems arise, we usually stop the medication. Like other beta-blocker drugs, atenolol can lead to constriction of the airways in individuals with a history of asthma. If cough or wheezing develops soon after starting the drug, it may need to be stopped. For those with mild asthma, our impression has been that an inhaled steroid (eg, Pulmicort, Flovent) may allow patients to tolerate the beta-blocker without increased airway reactivity. Atenolol can also cause emotional depression. Atenolol is less likely than other beta-blocker drugs (such as propranolol [Inderal]) to lead to nightmares, confusion, and hallucinations. Atenolol and other beta-blocker drugs can interfere with the body's ability to correct low blood sugar, so the drug must be used with extreme caution (if at all) in diabetics. The activity of the drug can be decreased when it is used in conjunction with non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin). We recommend that beta-blockers be discontinued 2-3 days before surgery because it can interfere with the action of epinephrine if that drug is needed to treat an allergic reaction during surgery.

Doses: The usual starting dose of atenolol for older adolescents and adults is 12.5-25 mg per day, but doses of up to 100 mg per day are used. For those with NMH, we usually aim for 1 mg of atenolol for every kg of body weight. For example, an individual weighing 62 kg (136 lb) would likely do well with between 50 and 75 mg of medication per day. People are unlikely to tolerate higher doses if their resting heart rate is below 50 beats per minute. The ideal dose for those with POTS is not well defined, and some authorities believe that lower doses may be preferable. Further study is needed to determine whether patients would do better with one form of beta blocker (selective beta blocker like atenolol) versus another (non-selective beta-blocker like propranolol).

Use in pregnancy: consult with your health care provider.

3. STIMULANTS

Brand names: Ritalin, Dexedrine, Adderall, and others. No studies have compared the relative efficacy of one to the others for those with NMH or POTS.

Indications: NMH or POTS

Action: The stimulant medications available for the treatment of attention deficit disorder are effective as vasoconstrictor drugs for the treatment of NMH and POTS. By improving constriction of blood vessels in the peripheral circulation, they improve the amount of blood flow returning to the heart. These medications may also exert their beneficial effects through actions on the central nervous system as well.

Doses: The maximum dose depends on the individual's weight. We begin with low doses, increasing once it is clear the patient tolerates the drug.

Dextroamphetamine: Dexedrine spansules are the sustained release form of the medication, and because they usually contain no milk protein they are among the ones we use for patients with milk allergy. The average starting dose for adolescents and adults is one 5 mg Dexedrine spansule each morning for 3 days or so. If there is no apparent improvement at this dose by that time, we increase the dose to two of the 5 mg spansules in the morning (at the same time). After another 3-4 days, if there is no improvement, increase to 3 spansules (15 mg) in the morning. The top dose is different for each person, and further increases may be needed.

Methylphenidate: the dose of methylphenidate depends on the individual's weight, but we usually try to keep the dose below approximately 0.5 mg per kg of body weight. We begin with low doses, increasing once it is clear the patient tolerates the drug. The starting dose for school-age children as well as adolescents and adults is 5 mg, given first thing in the morning, repeated if necessary 4 hours later. Unless the 5 mg once or twice daily is enough to control symptoms, we recommend increasing the dose to one of the following:

- 10 mg in the AM and 4 hours later
- 10 mg in the AM, 5 mg four hours later
- 10 mg in the AM, 5 mg four hours later, and 5 mg four hours after the 2nd dose

The maximum dose can be substantially higher, up to about 1 mg of drug for every kg of body weight, but a dose of as little as 5 mg per day may be all that is required. One adolescent, for example, had her best response on a regimen of 15 mg per dose given three times a day.

Expected therapeutic effects: The short-acting forms of methylphenidate or dextroamphetamine usually start to take effect after 30-45 minutes or so, and the duration of effect is usually 4 hours or so. If the stimulant medications are working at a particular dose, we expect individuals to feel less lightheadedness, headache, or fatigue. There may also be improvement in the ability to concentrate and stay on task. Individuals usually know soon after

taking the first few doses if the drug is having a beneficial effect at that dose. The stimulants are controlled substances, so the prescriptions have to be written more frequently, and physicians cannot ask for refills on the same prescription.

Side effects: The main side effects of the stimulants are insomnia, a reduction in appetite, moodiness, and occasionally abdominal pain. Some patients describe increased lightheadedness, agitation, and other bothersome symptoms. If these develop, we usually stop the drug and move on to other medication trials.

Comment: We have found these medications to be particularly helpful for those who had a history of hyperactivity or attention deficit disorder in childhood, or a family member with the disorder, either alone or in combination with other NMH treatments.

Use in pregnancy: consult with your health care provider.

4. MIDODRINE

Brand name: ProAmatine

Type of drug: Midodrine is classified as an alpha-1 agonist, or vasoconstrictor drug. Unlike the stimulant drugs, it is not thought to have direct central nervous system effects.

Action: The main effects of midodrine are to cause blood vessels to tighten, thereby reducing the amount of blood that pools in the abdomen and legs, shifting that blood volume into the central circulation where we want it to be. The drug has been used in thousands of individuals around the world, and appears to be well tolerated.

Side effects: The main side effects from midodrine in those with orthostatic hypotension (a condition similar to, but not the same as, neurally mediated hypotension) are: high blood pressure when lying down in 15-20%, itching (also called pruritis) in 10-15%, pins and needles sensation in 5-10%, urinary urgency/full bladder in 5%.

Common side effects to be expected include a sense of the scalp tingling, and the hair on the arms and neck standing on end. These changes are signs that the drug is working, and are not reasons to discontinue the drug. Adolescents and young adults with NMH and POTS should not be at risk for the same degree of high blood pressure as those with orthostatic hypotension (whose average age is closer to 50-60 years), but one needs to watch for this.

Dose: A conservative starting dose for midodrine is 2.5 mg three times daily to ensure that the dose is tolerated. The first dose should be taken upon awakening in the morning, then 4 hours later, and then 4 hours after that (e.g., 8AM, 12N, 4PM). A reasonable dose progression follows:

2.5 mg three times a day for 2-7 days (Each dose taken approximately 4 hours apart).
5.0 mg three times a day for 2-7 days
7.5 mg three times a day for 2-7 days
10.0 mg three times a day

If there is substantial improvement at a lower dose, then it may be wise to stay at this dose for a longer period. It is not always necessary to march up to the 10 mg three times a day dose. The drug effect lasts only about 3-4 hours, so the medication may need to be spaced differently once it is clear that it is having a beneficial effect. Occasional patients benefit from up to 15 mg per dose.

Comment: As a general rule, midodrine and stimulants should not be prescribed together, as the combination can lead to excessive blood pressure elevations. We generally attempt to stop stimulant medications before starting midodrine.

Use in pregnancy: consult with your health care provider.

5. SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Brand names: The selective serotonin re-uptake inhibitor (SSRI) medications most commonly used for those with NMH or POTS are Zoloft, Prozac, and Lexapro, but others in this class of antidepressant medications are likely to work as well.

Action: The SSRI medications inhibit the reuptake of serotonin at nerve terminals, leaving more serotonin available as a neurotransmitter. Serotonin can have a vasoconstricting effect on blood vessels.

Doses: The doses used to treat NMH or POTS are similar to those used for the treatment of depression; as with the other medications for NMH and POTS, it makes sense to start at a low dose and to increase gradually (allowing 2-4 weeks for the medication to begin working after a particular dose increase).

With Zoloft, for example, we usually begin with a dose of 12.5 - 25 mg per day, increasing to 50 mg per day if needed after 2-4 weeks, then adjusting upwards depending on the response.

With Lexapro, the starting dose is 5 mg per day for 2-4 weeks, then increasing to 10 mg per day if needed. Further gradual increases may be warranted after another month.

Side effects: Some patients describe worse orthostatic intolerance (lightheadedness, fainting) or

worse fatigue on the SSRIs. If these symptoms occur, we usually stop the drug. Other side effects that can occur include increased bruising, sweating, reduced libido, diarrhea or nausea, or insomnia.

Comment: These medications may be especially helpful in patients with increased anxiety or depressed mood, as their primary use is for treating these symptoms, but one does not need to have either anxiety or depression for the SSRIs to help with NMH or POTS.

One of the recent areas of concern about this class of medications has related to the rare but serious risk of suicide in the first 1-2 weeks after starting these medications. The evidence suggests that this risk is primarily seen in those who are severely depressed. In these individuals, who have suicidal thoughts but are too apathetic and sluggish to act upon them, the SSRI medications can have an early activating effect. As a result, patients can have improved energy for the first 1-2 weeks after starting the SSRI medications, but this improved energy occurs before their moods improve. Until mood improves, the individual who remains suicidal has the energy to act upon those impulses. The risk of suicide and major personality changes drops markedly after 2 weeks or so. Be alert to the potential for unusual reactions, and stop the medication and check in with your physicians if you have concerns about how things are going.

Use in pregnancy: Several studies suggest that SSRI medications are not associated with an increased risk of birth defects, but use of SSRI medications late in pregnancy can be associated with a withdrawal syndrome in newborns (usually mild and transient), as well as with a risk of pulmonary hypertension in the newborn. More data are appearing on these issues, so consult with your health care provider.

6. DISOPYRAMIDE

Brand name: Norpace

Type of drug: an anti-arrhythmic, anti-cholinergic drug

Indication: NMH (no studies in POTS)

Action: Norpace blocks the response to adrenaline (epinephrine), and prevents the forceful heart contractions that occur in neurally mediated hypotension.

Side effects: Some individuals complain of headaches or fatigue after Norpace, and others have worse lightheadedness. Other possible side effects are dry mouth, constipation, blurred vision, and impaired urination. This drug can activate glaucoma in some individuals. Norpace should not be taken with erythromycin, clarithromycin, azithromycin, phenothiazines, trimethoprim-sulfamethoxazole, cisapride, or other Class 1a anti-arrhythmic agents because of the potential for triggering serious heart rhythm abnormalities. For similar reasons, it should be used with great caution in those on tricyclic antidepressants. Due to its ability to reduce the forcefulness of the

heart's pumping action and to trigger arrhythmias, its use should be considered very carefully in those with heart disease. Use of the drug by those already taking beta-blockers or calcium channel blockers requires similar caution.

Doses: typically the dose for older adolescents and adults is 100-200 mg of the CR (sustained release) preparation twice daily, although higher doses are sometimes tolerated, and lower doses are sometimes effective. It is preferable to take it on an empty stomach, an hour before or two hours after eating, but it can be taken with food to reduce stomach irritation. Some individuals with medication sensitivities need to have the drug started at 100 mg each morning for a week, with increases of 50 or 100 mg per week (using the 150 mg CR capsule).

Use in pregnancy: Consult with your health care provider.

7. CLONIDINE

Brand name: Catapres

Type of drug: a selective antagonist of alpha-2 adrenergic receptors.

Indication: NMH or POTS

Action: Clonidine is an anti-hypertensive that reduces sympathetic nervous system outflow from the brain. It can lead to an expansion of blood volume in a subset of those with orthostatic intolerance. It is also used as a drug for those with attention deficit disorder, and has been reported to help reduce anxiety, reduce withdrawal symptoms in those who are on narcotic medications, and improve sleep when taken at night. There is also some evidence that it can improve stomach emptying in patients with delayed gastric motility. We have found that a proportion of patients with CFS benefit from it.

Side effects: Side effects can include worse fatigue and lightheadedness (due to the anti-hypertensive effect), and dry mouth. If side effects are mild in the first week, we usually ask patients to continue the drug to see if these effects resolve and the therapeutic benefit becomes evident over the next few weeks. If side effects are more impressive, we suggest stopping it.

If people have been taking clonidine for a prolonged period of time, they need to wean off it slowly to avoid developing rebound hypertension.

Occasional patients for whom clonidine appeared helpful for several months have developed worse side effects later, consisting of hot flashes, low blood pressure, and worse fatigue. In such instances it is often wise to consider withdrawing clonidine gradually to see whether it is contributing to problems.

Doses: typically the starting dose for older adolescents and adults is ½ a tablet (0.05 mg) at night

for 3-7 days, then increasing to a full 0.1 mg tablet at night. Higher doses are sometimes tolerated.

Comment: For those who are allergic to milk protein the Mylan brand form is lactose free.

Use in pregnancy: Consult with your health care provider.

8. PYRIDOSTIGMINE BROMIDE

Brand name: Mestinon

Type of drug: acetylcholinesterase inhibitor

Indication: NMH or POTS

Action: Pyridostigmine bromide (Mestinon) is a medication that has been used for decades to treat a neuromuscular condition, myasthenia gravis, and it is also used to prevent damage from certain nerve gases during chemical warfare. Its action is to interfere with the breakdown of acetylcholine, a neurotransmitter, thereby making more acetylcholine available at nerve and muscle interfaces. Greater concentrations of acetylcholine in the autonomic nervous system would be expected to result in a lower heart rate. In several studies, Mestinon was recognized to cause a slowing of heart rate. This response led some to postulate that it might be helpful for those with neurally mediated hypotension or syncope (NMH) and postural tachycardia syndrome (POTS). Formal study has confirmed those hypotheses, and the drug has been shown to have a therapeutic benefit for some people with POTS and NMH, mainly by increasing the amount of parasympathetic tone in the autonomic nervous system.

Side effects: Mestinon is generally well tolerated, but the most common side effects are nervousness, muscle cramps or twitching, nausea, vomiting, or diarrhea, stomach cramps, increased saliva, anxiety, and watering eyes. Notify your physician if these are occurring, and if the side effects are more bothersome, stop the drug. The most serious side effects are skin rash, itching, or hives, seizures, trouble breathing, slurred speech, confusion, or irregular heartbeat. Because Mestinon can lower heart rate, it needs to be used with caution (and started at a low dose) in those whose heart rates at rest are in the 50-60 beats per minute range, and in those taking beta-blocker drugs (atenolol, propranolol, metoprolol, and others). The drug can increase bronchial secretions in those with asthma, so it should be taken with caution in affected asthmatics. Magnesium supplements can occasionally cause problems when taking Mestinon, so these should be stopped when Mestinon is started.

Doses: In adolescents and adults with POTS and NMH, we have been using this dosage schedule, using the 60 mg pills or the 60 mg/5mL oral solution:

Day 1-3: 30 mg once daily

Day 4-7: 30 mg twice daily (6-7 AM, 4PM)
Day 8-10: 60 mg AM, 30 mg PM
Day 11 onward: 60 mg twice daily

For those who have been home-bound, a more gradual increase in doses is warranted, and doses can be increased by 30 mg weekly. Some patients may benefit from lower doses of 30 mg once or twice daily, and if a good response is achieved at a low dose, there is no need to increase further. Occasional patients benefit from a third dose during the day (morning, mid-day, bedtime), and one adolescent found that 45 mg in the morning, 30 mg at noon and 15 mg at bedtime was ideal for her. Some patients with CFS have been reported to do better on small doses of just 12.5-30 mg once daily.

Use in pregnancy: Use of pyridostigmine should be avoided during pregnancy due to the possibility of adverse effects on the fetus.

BIBLIOGRAPHY

General overviews of CFS:

- Fukuda K, Straus SE, Hickie I, Sharpe M, Dobbins JG, Komaroff A, and the International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Int Med* 1994;121:953-9. [the current case definition]

Orthostatic intolerance (overviews):

- Grubb BP. Neurocardiogenic syncope. *N Engl J Med* 2005;352:1004-10.
- Kanjwal Y, Kosinski D, Grubb BP. The postural orthostatic tachycardia syndrome: definitions, diagnosis, and management. *PACE* 2003;26:1747-57.
- Medow MS, Stewart JM. The postural tachycardia syndrome. *Cardiology in Review* 2007;15:67-75.

Orthostatic intolerance (general):

- MacLean AR, Allen EV. Orthostatic hypotension and orthostatic tachycardia: treatment with the “head-up” bed. *JAMA* 1940;115:2162-7.
- Frohlich ED, Dunstan HP, Page IH. Hyperdynamic Beta-adrenergic circulatory state. *Arch Int Med* 1966;117: 614-9.
- Fouad FM, Tadena-Thome L, Bravo EL, et al. Idiopathic hypovolemia. *Ann Int Med* 1986;104:298-303.
- Streeten DHP, Anderson GH. Delayed orthostatic intolerance. *Arch Int Med* 1992;152:1066-72.
- Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: An attenuated form of acute pandysautonomia? *Neurology* 1993;43:132-7.
- Furlan R, Jacob G, Snell M, et al. Chronic orthostatic intolerance: a disorder with discordant cardiac and vascular sympathetic control. *Circulation* 1998; 98:2154-9.
- Jacob G, Costa F, Shannon JR, et al. The neuropathic postural tachycardia syndrome. *New Engl J Med* 2000;343:1008-14.
- Benditt DG, Padanilam B, Samniah N, et al. Catecholamine response during hemodynamically stable upright posture in individuals with and without tilt-table induced vasovagal syncope. *Europace* 2003;5:65-70.
- Brady PA, Low PA, Shen WK. Inappropriate sinus tachycardia, postural orthostatic tachycardia syndrome, and overlapping syndromes. *PACE* 2005;28:1112-1121.

Orthostatic intolerance and CFS:

- Rowe PC, Bou-Holaigah I, Kan JS, Calkins H. Is neurally mediated hypotension an unrecognised cause of chronic fatigue? *Lancet* 1995;345:623-4.
- Bou-Holaigah I, Rowe PC, Kan J, Calkins H. Relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA* 1995;274:961-7.
- Stewart JM, Gewitz MH, Weldon A, et al. Orthostatic intolerance in adolescent chronic fatigue syndrome. *Pediatrics* 1999;103:116-21.

- Stewart JM, Gewitz MH, Weldon A, et al. Patterns of orthostatic intolerance: the orthostatic tachycardia syndrome and adolescent chronic fatigue. *J Pediatr* 1999;135:218-25.
- Streeten DHP, Thomas D, Bell DS. The roles of orthostatic hypotension, orthostatic tachycardia, and subnormal erythrocyte volume in the pathogenesis of the chronic fatigue syndrome. *Am J Med Sci* 2000;320(1):1-8.
- Tanaka H, Matsushima R, Tamai H, Kajimoto Y. Impaired postural cerebral hemodynamics in young patients with chronic fatigue with and without orthostatic intolerance. *J Pediatr* 2002;140:412-7.
- Freeman R. The chronic fatigue syndrome is a disease of the autonomic nervous system. Sometimes. *Clin Auton Res* 2002;12:231-3.
- Wyller VB, Due R, Saul JP, et al. Usefulness of an abnormal cardiovascular response during low-grade head-up tilt-test for discriminating adolescents with chronic fatigue from healthy controls. *Am J Cardiol* 2007;99:997-1001.
- Wyller VB, Saul JP, Amlie JP, et al. Sympathetic predominance of cardiovascular regulation during mild orthostatic stress in adolescents with chronic fatigue. *Clin Physiol Funct Imaging* 2007;27:231-8.

Treatment of orthostatic intolerance:

- Bloomfield DM, ed. A symposium: A common faint: tailoring treatment for targeted groups with vasovagal syncope. *Am J Cardiol* 1999;84: 1Q-39Q.
- van Lieshout JJ, et al. Physical manoeuvres for combating orthostatic dizziness in autonomic failure. *Lancet* 1992;339:897-8.
- Rosen SG, Cryer PE. Postural tachycardia syndrome: Reversal of sympathetic hyperresponsiveness and clinical improvement during sodium loading. *Am J Med* 1982;72:847-50.
- Mahanonda N, et al. Randomized double-blind, placebo-controlled trial of oral atenolol in patients with unexplained syncope and positive upright tilt table test results. *Am Heart J* 1995;130:1250-3.
- Ward CR, et al. Midodrine: a role in the management of neurocardiogenic syncope. *Heart* 1998; 79:45-9.
- Qingyou Z, et al. The efficacy of midodrine in the treatment of children with vasovagal syncope. *J Pediatr* 2006;149:777-80.
- Zeng C, et al. Randomized, double-blind, placebo-controlled trial of oral enalapril in patients with neurally mediated syncope. *Am Heart J* 1998;136:852-8.
- Di Girolamo E, et al. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vaso-vagal syncope: a randomized, double-blind, placebo-controlled study. *JACC* 1999;33: 1227-30.
- Boehm KE, et al. Neurocardiogenic syncope: response to hormonal therapy. *Pediatrics* 1997;99:623-5.
- Grubb BP, et al. The use of methylphenidate in the treatment of refractory neurocardiogenic syncope. *PACE* 1996;19:836-40.
- Robertson D, et al. Clonidine raises blood pressure in severe idiopathic orthostatic hypotension. *Am J Med* 1983;74:193-200.

- Singer W, et al. Acetylcholinesterase inhibition in patients with orthostatic intolerance. *J Clin Neurophysiol* 2006;23:477-82.
- Filler G, et al. Pharmacokinetics of pyridostigmine in a child with postural tachycardia syndrome. *Pediatrics* 2006;118:e1563-8.
- Raj SR, et al. Acetylcholinesterase inhibition improves tachycardia in postural tachycardia syndrome. *Circulation* 2005;111:2734-40.

Other related papers:

- Rowe PC, Calkins H. Neurally mediated hypotension and chronic fatigue syndrome. *Am J Med* 1998;105:15S-21S.
- Rowe PC, Calkins H, DeBusk K, et al. Fludrocortisone acetate to treat neurally mediated hypotension in chronic fatigue syndrome: a randomized controlled trial. *JAMA* 2001;285:52-59.
- Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid- based formula. *Gastroenterology* 1995;109:1503-12.
- Rowe PC, Barron DF, Calkins H, et al. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr* 1999;135:494-9.
- Barron DF, Cohen BA, Geraghty MT, et al. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. *J Pediatr* 2002;141:421-5.
- Gazit Y, Nahir AM, Grahame R, Jacob G. Dysautonomia in the joint hypermobility syndrome. *Am J Med* 2003;115:33-40.
- Milhorat TH, Chou MW, Trinidad EM, et al. Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. *Neurosurgery* 1999;44:1005-17.
- Heffez DS, Ross RE, Shade-Zeldow Y, et al. Treatment of cervical myelopathy in patients with the fibromyalgia syndrome: outcomes and implications. *Eur Spine J* 2007;16:1423-33.
- Venbrux AC, Lambert DL. Embolization of the ovarian veins as a treatment for patients with chronic pelvic pain caused by pelvic vein incompetence (pelvic congestion syndrome) *Curr Opin Obstet Gynecol* 1999;11:395-99.
- Venbrux AC, Chang AH, Kim HS, et al. Pelvic congestion syndrome (pelvic venous incompetence): impact of ovarian and internal iliac embolotherapy on menstrual cycle and chronic pelvic pain. *J Vasc Interv Radiol* 2002;13:171-8.
- Sullivan SD, Hanauer J, Rowe PC, et al. Gastrointestinal symptoms associated with orthostatic intolerance. *JPGN* 2005;40:425-8.
- Terlouw A, Ruble K, Stapert AF, et al. Orthostatic intolerance in survivors of childhood cancer. *Eur J Cancer*. 2007;43:2685-90.
- Mack KJ, Johnson JN, Rowe PC. Orthostatic intolerance and the headache patient. *Seminars in Pediatric Neurology* 2010;17:109-16.

Web resources for providers, families, schools, patients:

The CFIDS Association of America website is an excellent source of updates, information on options for education, and other aspects of dealing with this chronic illness. They are at www.cfids.org

The Dysautonomia Youth Network of America has a helpful newsletter and advice for children and adolescents, at www.dynakids.org

The National Dysautonomia Research Foundation website is a good source of information on the autonomic nervous system and a number of disorders, including forms of orthostatic intolerance, at www.ndrf.org