

*Notes: This is the **fourth** in a series of 5 blog posts about COVID-19 and Autonomic Dysfunction. This a pre-publication release that will be featured in a major medical journal.*

Coronavirus Induces Oxidative Stress Leading to Autonomic Dysfunction Often With Delayed Symptom Onset

Heather L. Bloom, MD¹ and Joseph Colombo, PhD, DNM, DHS²

1. Electrophysiology, Atlanta Veterans Affairs Medical Center and Emory University Medical School, Atlanta, GA
2. Parasympathetic & Sympathetic Nervous System Consultant, Franklin Cardiovascular Associates, PA & Autonomic Dysfunction and POTS Center, Sewell, NJ, and Senior Medical Director & CTO, Physio PS, Inc., Atlanta, GA, dovetech@erols.com

Correspondence should be addressed to Dr. Colombo, dovetech@erols.com

THERAPY OPTIONS

In general, Oxidative Stress is treated with Antioxidants; more on this below in the Non-Pharmaceutical section. Non-pharmaceutical therapy is often the primary P&S therapy which may often be accelerated with pharmaceutical therapy. Often, once P&S balance is re-established, assuming no end-organ dysfunction, the P&S will carry forward independent of pharmaceutical therapy and only non-pharmaceutical, maintenance therapy may be required. This is typically in the form of Antioxidants to help maintain proper Antioxidant levels in the body. With chronic disease or disorder, as with aging, antioxidants are depleted in the body and production is slowed; therefore, supplemental therapy is needed.

Pharmaceutical Therapy Options

Pharmaceutical therapy options are recommended based on patient history [ⁱ]. In general they included the following. For SW, 2.5 mg Midodrine titrated slowly, as needed, from qd to tid. For Orthostatic Hypotension, including pre-clinical cases, the first dose is recommended around dinner, four hours before laying down, when BP tended to be lowest. For POTS patients, morning doses are recommended since symptoms are typically more significant at that time. Midodrine is contraindicated for patients with supine hypertension and for patients with resting BPs higher than 160/90 mmHg [ⁱⁱ]. Some patients do not respond to, or are contra-indicated for, Midodrine. While Northera is the recommended alternate, it is very expensive and 30 to 60 mg Mestinon, qd, is recommended as the first alternate. Only if patients are unresponsive to Mestinon is Northera considered, but still must be approved. Non-pharmaceutical alternates are discussed below. Low dose Fludrocortisone or Pseudoephedrine may be suitable adjunctives [ⁱⁱⁱ]. Note, if patients present with SW and high BP, the high BP is (at least in part) compensatory for the associated Orthostatic Hypotension. In these cases treating the Hypertension as the primary typically confounds the condition and may even cause BP to increase, as the poor brain perfusion is exacerbated and the body defeats the therapy. In most cases, relieving SW organically reduces BP [ⁱⁱ] and any remaining Hypertension may then be treated as the primary, once the patient's P&S nervous systems stabilize.

For PE low-dose anti-cholinergic therapy (very low dose antidepressant therapy) is recommended. For example, no more than 10.0 mg, qd, dinner Nortriptyline (primary) or 20mg, qd, Duloxetine (secondary) is recommended. Clinical doses of these pharmaceuticals will exacerbate the condition with additional symptoms. Often patients that present with long standing PE, who have been referred for Psych-eval and have been prescribed much higher doses

of these pharmaceuticals, or have been prescribed antidepressants for more than six months with little or no relief, no longer respond or tolerate the recommended low-dose anti-cholinergic therapy, and alternate therapies are needed. The primary alternate anti-cholinergic therapy recommended is “Low-and-Slow” exercise (see below) and was also recommended to help re-condition the heart muscle for improved cardiac output and thereby improved brain perfusion. The recommended anti-cholinergic therapy tends to have little effect on BP and helps to pattern sleep. If a more potent anti-cholinergic is needed and weight-gain is not a problem, 10.0 mg, qd, dinner Amitriptyline is recommended.

If PE presents with SE and with established Hypertension or Cardiovascular Disease, then low-dose or dose equivalent Carvedilol is recommended. Carvedilol treats all three simultaneously. It is not only a beta-blocker, but it is also an antioxidant [^{iv},^v].

Note, PE often causes secondary SE. SE may lead to hypertension. In these cases, treating the Hypertension as the primary exacerbates the Hypertension, similar to SW. In most cases, relieving PE organically relieves SE (after a few months) which, in turn, organically reduces BP [Error! Bookmark not defined.] and any remaining Hypertension may then be treated as the primary, once the patient’s P&S nervous systems stabilize.

For (stand) SE, therapy depends on the differential. If SE is demonstrated with PE indicating (pre-clinical) Vasovagal Syncope, then PE therapy is followed as the primary and typically the SE is relieved organically. If SE is demonstrated with a drop in HR from resting to stand indicating (pre-clinical) Neurogenic Syncope, volume building and often Midodrine helps to treat the stand SE. Any remaining SE indicates (by omission) possible Cardiogenic Syncope and more testing is required to diagnose and treat. [Error! Bookmark not defined.]

Autonomically mediated arrhythmia, with or without SE may be documented. Autonomically mediated arrhythmia is associated with inefficient circulation and may be another result of Oxidative Stress. Autonomically mediated arrhythmia with SE may contribute to Cardiogenic syncope, and treating SE may help to relieve the arrhythmia. Autonomically mediated arrhythmia with PE may contribute to Vasovagal Syncope, and treating SE may help to relieve the arrhythmia. Autonomically mediated arrhythmia with normal Sympathovagal Balance (SB = S/P, a resting baseline measurement), the arrhythmia is not autonomic and further testing maybe required to diagnose and treat. **[Error! Bookmark not defined.]**

Non-Pharmaceutical Therapy Options

In general, Psychosocial Stress reduction is recommended with history-specific Antioxidant and Nitric Oxide supplement recommendations to reduce Oxidative Stress and improve blood flow **[Error! Bookmark not defined.]**. Nitric Oxide also has Antioxidant properties. Non-Pharmaceutical therapy options are recommended if patients are intolerant or unresponsive to the pharmaceutical options.

Alpha-Lipoic Acid (ALA) and Co-Enzyme Q10 (CoQ10) are two of the most potent Antioxidants made in the body. ALA tends to be more selective for nerves. CoQ10 tends to be more selective for cardiac tissue. Both help to recycle other Antioxidants, including Vitamins A, C & E, and Glutathione. Specifically for SW, 600 mg tid, Alpha-Lipoic Acid, titrated as needed and tolerated ^[vi], is recommended. Exercise is arguably the most potent Antioxidant available. For PE (which is an autonomic state that amplifies the stress response of all stressors including healthy stressors such as exercise), six months of “Low-and-Slow” exercise is recommended to retrain the nervous system to accept small, healthy stresses before more significant stresses may be tolerated. Low-and-Slow exercise is characterized by walking at no more than 2 mph for 40

contiguous minutes per day, for 6 months (suitable alternates include slow motion rowing, or slow motion bicycling or pedaling are options) [Error! Bookmark not defined.]. Exercise that breaks down muscle or connective tissue or that raises HR and BP too fast should be strictly avoided. Often “Low-and-Slow” exercise is augmented, especially if the patient reported significant sleep difficulties, by 20 minutes of supine, 15° head-down posture around two hours before bed-time and up to three times per day, as needed, but in any instance, at least 2 hours after low-dose Midodrine dosing. Patients who are too lightheaded to sit up or too exercise intolerant may perform supine Low-and-Slow exercise by lying on the floor next to the bed with their lower legs on the bed, and only move their lower legs like they were walking at 2 mph, for the prescribed 40 minutes (see insert).

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KEY WORDS

Coronavirus, Parasympathetic, Sympathetic, Oxidative Stress, Antioxidants

ABBREVIATIONS

ALA	Alpha-Lipoic Acid
ANS	Autonomic Nervous System
CoQ10	Co-enzyme Q10
COVID-19	Coronavirus (SARS-CoV-2)
P&S	Parasympathetic and Sympathetic
PE	Parasympathetic Excess
POTS	Postural Orthostatic Tachycardia Syndrome

SE	Sympathetic Excess
SW	Sympathetic Withdrawal

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