Autonomic neuropathy: treatment

By Aziz I Shaibani MD (Dr. Shaibani of Baylor College of Medicine has no relevant financial relationships to disclose.)
Duaa Jabari MD (Dr. Jabari of the Mississippi Medical Center has no relevant financial relationships to disclose.)

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Introduction

Overview

Autonomic neuropathy has numerous causes, some of them common, such as diabetic autonomic neuropathy, and others rare, such as Fabry disease, but all can produce disabling symptoms. Autonomic neuropathy can affect the sympathetic, parasympathetic, and enteric branches of the autonomic nervous system to variable degrees, causing dysfunction of different organs such as heart, intestinal tract, and urinary bladder. In this article, the authors review the available symptomatic treatments of these dysfunctions, focusing mainly on orthostatic hypotension, postural orthostatic tachycardia syndrome (POTS), gastroparesis, bladder hypomotility, and erectile dysfunction. A brief physiological and pathophysiological review and a discussion of available treatments are included for each disease discussed.

Key points

• Although autonomic neuropathy can be disabling, the patient’s symptoms and quality of life can be improved efficiently.
• In general practice, postural orthostatic tachycardia syndrome (POTS) can be easily overlooked.
• New promising treatments are available for orthostatic hypotension, postural orthostatic tachycardia syndrome, and gastroparesis.

Orthostatic hypotension

Pharmacotherapy of orthostatic hypotension.

Physiology and pathophysiology. Orthostatic hypotension is the most incapacitating symptom of autonomic failure. Severely afflicted patients are unable to leave the supine position without experiencing symptoms of presyncope or losing consciousness. Baroreceptor reflexes maintain hemodynamic stability in response to postural change. These reflexes depend on blood pressure information from the aortic arch and the carotid sinus, which enters the brain in the IX and X cranial nerves. The hallmark of neurogenic orthostatic hypotension is the failure to release norepinephrine appropriately on standing. Patients with neurogenic orthostatic hypotension due to pure autonomic failure or an autonomic peripheral neuropathy typically have lower resting norepinephrine levels, due to degeneration of the post-ganglionic neurons, although intersubject variability limits the use of this measure as a diagnostic test (Goldstein et al 2003).

Treatment of orthostatic hypotension.

Nonpharmacological measures. Patient education is the cornerstone of the management of orthostatic hypotension. Patients with orthostatic hypotension should move from a supine to standing position in gradual stages particularly in the morning, when orthostatic tolerance is lowest (Omboni et al 2001). A number of physical maneuvers can help maintain blood pressure during daily activities such as leg crossing, stooping and squatting (van Lieshout et al 1992). The excessive natriuresis and reduction in central blood volume can be attenuated or minimized by increasing sodium intake with high-sodium containing foods or salt tablets. Raising the head of the bed 10 degrees to 20 degrees activates the renin-angiotensin-aldosterone system and decreases the nocturnal diuresis (MacLean and Allen 1940).

The use of custom fitted elastic stockings permit the application of a graded pressure to the lower extremity and abdomen. It is essential that such stockings extend to the waist as most peripheral pooling occurs in the splanchnic circulation. These stockings are poorly tolerated by many patients, particularly those with painful peripheral neuropathies or motor dysfunction.

Pharmacological measures. Numerous agents from diverse pharmacological groups have been implemented in the treatment of orthostatic hypotension (see Table I). The therapeutic goal is merely to ameliorate all symptoms while
Table 1. Pharmacotherapy of Orthostatic Hypotension

**Mineralocorticoids**

- 9 alpha-fludrocortisone

**Sympathomimetic agents**

- Midodrine
- Ephedrine
- Pseudoephedrine
- Phenylephrine
- Methylphenidate
- Dextroamphetamine
- Tyramine (with monoamine oxidase inhibition)
- Clonidine
- Yohimbine
- Droxidopa

**Acetylcholinesterase inhibitors**

- Pyridostigmine

**Nonspecific pressor agents**

- Ergot derivatives
- Caffeine
- Somatostatin analogues

**Beta-adrenergic blocking agents**

- Propranolol
- Pindolol
- Xamoterol
- Prenalterol

**Prostaglandin synthetase inhibitors**

- Indomethacin
- Flurbiprofen
- Ibuprofen
- Naproxen

**Dopamine blocking agents**

- Metoclopramide
- Domperidone

**V1 and V2 receptor agonists**

- Desmopressin acetate (DDAVP)
- Lysine-vasopressin
- Erythropoietin

**Agents to increase central blood volume.**

9-alpha-fluorohydrocortisone. 9-alpha-fluorohydrocortisone (fludrocortisone acetate), a synthetic mineralocorticoid, can be used to supplement the increase in dietary fluids and salt (Hickler et al 1959). This agent has a long duration of action and is well-tolerated by most patients. Fludrocortisone increases the blood volume and may enhance the sensitivity of blood vessels to circulating catecholamines (Hickler et al 1959; Davies et al 1978). Treatment is initiated with a 0.1 mg tablet daily. Little benefit is obtained by increasing beyond 0.3 to 0.5 mg. Treatment may be limited by supine hypertension due to an increase in the peripheral vascular resistance (Chobanian et al 1979). Other side effects include ankle edema, hypokalemia and rarely congestive heart failure. Potassium supplementation is usually required, particularly when higher doses are used. Adequate salt and water intake are also important and may obviate the need for this agent in milder cases.
Agents to increase peripheral vascular resistance.

**Vasopressin analogues.** The synthetic vasopressin analogue desmopressin acetate (DDAVP) may also be used to enhance fluid retention in patients with orthostatic hypotension. DDAVP, which can be taken as a nasal spray (10 to 40 mcg) or orally (100 to 800 mcg), may prevent the nocturia and weight loss, and it reduces the morning postural fall in blood pressure in patients with autonomic failure. Fluid and electrolyte status should be carefully monitored during therapy to avoid hyponatremia (Mathias et al 1986). Lower doses (5 mcg intranasally) may be clinically effective and avoid these side effects (Sakakibara et al 2003).

**Sympathomimetic agents.** A direct or indirect sympathomimetic agent may be used in conjunction with central blood volume supplementation should the patient remain symptomatic (Jordan et al 1998). The available alpha-1 adrenoreceptor agonists include those with direct and indirect effects (eg, ephedrine and pseudoephedrine), those with direct effects (midodrine, phenylephrine) and those with only indirect effects (eg, methylphenidate and dextroamphetamine sulphate). Ephedrine (25 to 50 mg, 3 times a day) and pseudoephedrine (30 to 60 mg, 3 times a day) are now the most frequently prescribed indirectly acting agents.

The peripheral selective alpha-agonist, midodrine, is approved by the FDA for the treatment of orthostatic hypotension. The pressor effect of midodrine is due to both arterial and venous constriction. The efficacy of this agent has been demonstrated in open-label and double-blind studies (Freeman 1996; Low et al 1997). Midodrine, the prodrug is activated to deglymidodrine the active alpha-receptor agonist. Patient sensitivity to this agent varies, and the dose should be titrated from 2.5 to 10 mg 3 or 4 times a day (Wright et al 1998). Potential side effects of this agent include pilomotor reactions, pruritus, supine hypertension, gastrointestinal complaints, and urinary retention. This agent does not cross the blood brain barrier and central nervous system side effects occur infrequently (McTavish and Goa 1989; McClellan et al 1998). There are few head-to-head comparisons of the alpha-adrenoreceptor agonists. In a small clinical trial midodrine (mean dose 8.4 mg, 3 times daily) improved standing blood pressure and orthostatic tolerance more than ephedrine (22.3 mg, 3 times daily) (Foud-Tarazi et al 1995).

**Atomoxetine,** a norepinephrine reuptake inhibitor, has been studied as a therapy for orthostatic hypotension. One study looked at the short term-effect of this medication (up to 60 minutes) and showed increase in seated and standing systolic blood pressure in patients with central (but not peripheral) autonomic failure. Of note, the mean seated pressure was in the hypertensive range (Shibao et al 2007). In comparison to the short-term effect of midodrine, atomoxetine was found to be superior in producing greater pressor response in upright position and improving symptoms (Ramirez et al 2014). The long-term safety and efficacy of this medication needs to be studied.

Droxidopa (L-threo dihydroxyphenylserine, L-DOPS), a synthetic amino acid precursor of the neurotransmitter and hormone norepinephrine, has been approved for use in Japan since 1989; the United States FDA approved this medication in February 2014 for treatment of neurogenic orthostatic hypotension. Droxidopa was found to be well tolerated in long-term use in a study of 350 patients who received 100 to 600 mg 3 times daily of droxidopa for an average of 363 days. Most reported adverse reactions, including cardiovascular ones, were not attributed to the medication (Isaacscon et al 2016).

**Cholinesterase inhibitors.** Pyridostigmine improves standing blood pressure in patients with orthostatic hypotension without aggravating supine hypertension (Singer et al 2006). Pyridostigmine (60 mg three times daily) can be used with or without low dose of midodrine (5 mg), which could provide more potent and more sustained pressor response. The greatest effect is on diastolic blood pressure, suggesting that the improvement is due to increased total peripheral resistance. The proposed mechanism is that by enhancing ganglionic transmission, pyridostigmine augments baroreflex-mediated increases in systemic resistance proportional to the magnitude of orthostatic stress.

Agents to increase red cell mass.

**Erythropoietin.** Erythropoietin increases standing blood pressure and improves orthostatic tolerance in patients with orthostatic hypotension (Hoeldtke and Streeten 1993; Perera et al 1995). This agent corrects the normochromic normocytic anemia that frequently accompanies autonomic failure. Recombinant human erythropoietin is administered subcutaneously or intravenously at doses between 25 U to 75 U per kilogram three times a week until a hematocrit that approaches normal is attained. Lower maintenance doses (approximately 25U per kilogram three times a week) may then be used. Iron supplementation is usually required, particularly during the period when the hematocrit is increasing. The mechanism of action for the pressor effect of this agent is unresolved (Hoeldtke and Streeten 1993).
However, concerns of excessive supine hypertension and increased cardiovascular and cerebrovascular disease risk have reduced the use of this agent for neurogenic orthostatic hypotension.

**Other agents.** A list of other agents that have been used in the treatment of orthostatic hypotension is present in Table 1.

**Postural orthostatic tachycardia syndrome (POTS).** POTS is defined as the development of orthostatic symptoms associated with a heart rate increment of 30 or greater, usually to 120 bpm or greater without orthostatic hypotension.

Pathophysiology mechanisms include peripheral denervation, hypovolemia, venous pooling, beta receptor supersensitivity, psychological mechanisms, and presumed impairment of brain stem regulation. These different mechanisms result in different types of POTS. The most common types are neuropathic POTS, hyperadrenergic POTS, and POTS with deconditioning. Hyperadrenergic POTS shows BP increase on standing and elevated norepinephrine level, which differs from neuropathic POTS that lacks these features. Patients can benefit from pathophysiologically based regimen of management (Low et al 2009). All patients with POTS require a high salt diet, copious fluids, and postural training. Many require beta receptor antagonists in small doses and low-dose vasoconstrictors. In a study by Lai and colleagues, treatment with both midodrine and beta blockers was associated with overall improvement in POTS patients’ general health (Lai et al 2009). Midodrine is probably an effective treatment for neuropathic but not for hyperadrenergic POTS (Ross et al 2014). A study conducted at Vanderbilt University showed that low-dose oral propranolol significantly attenuated tachycardia and improved symptoms in POTS (Raj et al 2005). There was also an improvement in symptom burden with this therapy. Octreotide was also studied as a treatment for POTS and orthostatic intolerance. In a comparison of midodrine and octreotide, both of them suppressed tachycardia in POTS and improved standing times in orthostatic intolerance (Hoeldtke et al 2006). The 2 drugs had similar potencies; combination therapy was not significantly better than monotherapy.

Octreotide might be effective in refractory cases of POTS and orthostatic hypotension that do not respond to other medications. In a study performed by Kanjwal and colleagues, a small group of patients (12) with refractory orthostatic intolerance who did not respond to any other therapeutic modality were started on octreotide (Kanjwal et al 2012). Six out of twelve patients reported symptomatic improvement. Standing heart rate was significantly reduced whereas systolic blood pressure was increased in 5 patients. (Blood pressure and heart rate data before and after octreotide administration were available from these 5 patients only). A randomized controlled study is needed to verify these findings.

Coffin and colleagues found that acute use of desmopressin significantly attenuated tachycardia and improved symptoms in POTS (Coffin et al 2012). Safety with chronic use (with hyponatremia being the main concern) needs further evaluation.

**Bowel hypomotility**

**Treatment of bowel hypomotility.**

**Physiology and pathophysiology.** The autonomic control of the gastrointestinal tract is mediated by the extrinsic parasympathetic and sympathetic nervous systems and the intrinsic enteric nervous system. The post-synaptic cholinergic neurons provide excitatory input to the gastrointestinal tract whereas the sympathetic nervous system provides inhibitory input to the gastrointestinal tract (Goyal and Hirano 1996; Kunze and Furness 1999; Furness 2000).

The enteric nervous system is comprised of a myenteric plexus located between the inner-circular and outer-longitudinal smooth muscle layers (Auerbach plexus) and a submucosal plexus (Meissner plexus). Numerous intrinsic enteric neurons have been identified, and any individual neuron may contain multiple neuropeptides. Even in the absence of extrinsic autonomic nervous system influences, the enteric nervous system governs basic gut functions (Goyal and Hirano 1996; Kunze and Furness 1999; Furness 2000).

The degeneration of both extrinsic and intrinsic autonomic neurons in patients with autonomic failure results in symptoms of gastrointestinal dysfunction that involve both the upper and the lower gastrointestinal tract (Chelimsky et al 1996; Winge et al 2003). The symptoms of upper gastrointestinal autonomic dysfunction are exemplified by the features of gastroparesis diabeticorum: abdominal bloating, post-prandial fullness, early satiety, nausea and vomiting.
occur commonly in diabetic patients. Constipation, abdominal fullness and fecal incontinence are the hallmarks of lower gastrointestinal tract dysfunction. The constipation may alternate with diarrhea, particularly in patients with diabetic autonomic neuropathy.

**Pharmacotherapy of diabetic gastroparesis.** In these patients, glucose control should be optimized as hyperglycemia may delay gastric emptying. The prokinetic agents, metoclopramide, erythromycin, domperidone and cisapride are the primary pharmacological agents used to treat this disorder. These agents enhance gastric emptying and improve the symptoms of gastroparesis.

The benzamide, metoclopramide (5 to 20 mg orally, 30 minutes before meals and at bedtime), accelerates gastric emptying and also has a central antiemetic action. The prokinetic effects are due to augmented release of acetylcholine from enteric cholinergic neurons (due to activation of 5-HT4 receptors) and dopamine (D2) receptor antagonism. The central antiemetic effects of metoclopramide are mediated by dopamine (D2) receptor and serotonin (5-HT3) receptor antagonism in the area postrema of the periaqueductal gray. Patients maintained in the long term on metoclopramide may be at risk for the development of tardive dyskinesia and other dopamine-antagonist-related side effects (Camilleri 2002; Horowitz et al 2002; Talley 2003).

Erythromycin, administered both orally (250 mg, 3 times daily) and intravenously (3 mg/kg every 8 hours), improves gastric emptying and gastroparetic symptoms. This agent and related macrolide compounds exhibit strong in vitro affinity for motilin receptors, and have agonist properties that mimic the prokinetic action of exogenous motilin, a gastrointestinal polypeptide (Camilleri 2002; Horowitz et al 2002; Talley 2003).

Domperidone is a D2 receptor antagonist that does not cross the blood brain barrier. Efficacy in the treatment of gastroparesis has been demonstrated in several clinical trials. Although this drug has no central anti-dopaminergic effects, some central antiemetic effects may be due to activity in the area postrema. This agent is not available in the United States (Camilleri 2002; Horowitz et al 2002; Talley 2003).

Studies have focused on the promising use of ghrelin agonist (intravenous medication) in severe gastroparesis. It substantially reduces the frequency and severity of nausea and vomiting as well as overall gastroparesis symptoms, supporting further investigation of its use in the management of severe gastroparesis (Wo et al 2011). Oral ghrelin agonist resulted in reduction of gastroparesis symptoms whereas subcutaneous agonist showed symptomatic improvement and accelerated gastric emptying at 1 and 2 hours, but neither medication showed significant change in the primary endpoint (gastric half-emptying time) (Ejskjaer et al 2013; Shin et al 2013).

Studies of gastric pacing have not produced consistent results in patients with diabetic gastroparesis (Camilleri 2002; Horowitz et al 2002; Talley 2003).

**Gastric electrical stimulation.** Gastric electrical stimulation utilizes series of electric pulses to stimulate the stomach to contract. These pulses are produced by an implantable device, which consists of electrodes sutured to the muscular layer of the stomach and connected to a pulse generator implanted in a subcutaneous pocket in the abdominal wall. Gastric electrical stimulation can lessen symptoms of gastroparesis and frequency of vomiting within 6 weeks (McKenna et al 2008). This therapy is a low morbidity treatment option that may help patients whose symptoms fail to improve with medical therapy. A clinical trial showed that gastric electrical stimulation improved gastroparetic symptoms at 6 months with a sustained response at 12 months. Gastric emptying at 2 hours was also significantly reduced (Brody et al 2008). Another study showed that gastric electrical stimulation therapy significantly improved subjective and objective parameters in patients with severe gastroparesis; efficacy was sustained for up to 10 years and was accompanied by good safety and tolerance profiles (McCallum et al 2011).

Furthermore, gastric electrical stimulation was found to improve basal unstimulated gastric frequency (on electrogastrogram) to near normal after few years of use. This may indicate gastric remodeling with long-term use of gastric electrical stimulation (Williams et al 2013).

**Gastric per-oral endoscopic myotomy (endoscopic pyloromyotomy).** Gastric per-oral endoscopic myotomy has been utilized in refractory gastroparesis with promising results. In one study, 30 patients underwent this procedure, and the clinical response was seen in 86% of patients. Gastric emptying scan was repeated in 17 patients after the procedure, and it normalized or improved in 14 patients (Khashab et al 2017).

**Pharmacotherapy of bowel hypomotility.** An increase in dietary fiber (up to 25 g/day), with water (10 ounces four
times per day) and exercise is the first line of therapy for most patients. The use of psyllium (up to 30 g/day) or methylcellulose (up to 6 g/day) with a concomitant increase in fluid intake will further increase stool bulk. These agents and fiber should be increased gradually and concomitantly with an increase in fluid ingestion.

Stool softeners (eg, docusate sodium 100 to 500 mg/day) or lubricants (eg, mineral oil) together with an osmotic laxative (eg, lactulose 15 to 60 ml/day) may be used if the above measures are ineffective. Glycerin suppositories or sodium phosphate enemas stimulate evacuation by promoting fluid retention in the rectum (see Table 2).

Table 2. Pharmacotherapy of Bowel Hypomotility

**Bulk agents**
- Bran
- Psyllium
- Methylcellulose

**Laxatives and cathartics**
- Osmotic laxatives and cathartics
  - Lactulose
  - Sorbitol
  - Magnesium salts
  - Sodium phosphate
  - Polyethylene glycol-saline solutions
  - Glycerin suppositories
- Contact cathartics
  - Diphenylmethane derivatives
    - Phenolphthalein
    - Bisacodyl tablets or suppositories
  - Anthraquinone derivatives
    - Senna
    - Cascara
  - Ricinoleic acid (castor oil)

**Stool softeners and lubricants**
- Mineral oil
- Docusates

**Prokinetic agents**
- Metoclopramide
- Cisapride
- Domperidone
- Erythromycin
- Cholinomimetics
  - Bethanechol
  - Acetyl-cholinesterase inhibitors
- Opioid antagonists
- Misoprostol

The contact cathartics such as the diphenylmethane derivatives (phenolphthalein and bisacodyl), the anthraquinone (senna and cascara) should be used sparingly, although the use of these agents often cannot be avoided in patients with constipation due to severe autonomic failure. Extensive use of these agents may damage the myenteric plexus producing cathartic bowel. Other agents that may be helpful include the synthetic prostaglandin E1 analog, misoprostol, the neurotrophin, NT3, and the 5-HT4 partial agonist, tegaserod (Rao 2003; Winge et al 2003).

**Bladder hypomotility**

**Treatment of bladder hypomotility.**

**Physiology and pathophysiology.** The bladder wall is comprised of 3 layers of interdigitating smooth muscle and serves as a receptacle for the storage and appropriate evacuation of urine. This smooth muscle, the **detrusor muscle**, forms...
the internal sphincter at the junction of the bladder neck and urethra whereas the external sphincter is formed from the striated muscle of the urogenital diaphragm and is a true anatomical sphincter. The bladder has parasympathetic, sympathetic, and somatic innervation (Fowler 1999).

Pharmacotherapy of bladder hypomotility. Initial therapy should emphasize timed voiding schedules with bladder contractions enhanced by a Valsalva maneuver and Crede maneuver. Clean intermittent self-catheterization, however, is the primary therapy for impaired or absent detrusor muscle activity. The interval between catheterizations should be designed to maintain a residual volume of less than 100 cc and avoid incontinence. The majority of patients performing self-catheterization will develop bacteruria; however, antibiotic therapy is only necessary if symptomatic urinary tract infections occur (Fowler 1999).

Pharmacotherapy has a limited role in the treatment of detrusor areflexia. Stimulation of muscarinic, postganglionic receptors results in enhanced bladder contractility. Bethanechol chloride is a parasympathomimetic drug with relatively selective action at the urinary bladder. This agent may be effective in chronic states of detrusor atony or hypotonicity (Wein et al 1992). Typical oral doses range from 25 to 100 mg 4 times daily (Wein et al 1992).

Pharmacotherapy of erectile dysfunction.

Treatment of erectile dysfunction.

Physiology and pathophysiology. Cholinergic and noncholinergic nonadrenergic neurotransmitters mediate erectile function by relaxing the arterial and trabecular smooth muscle of the corpus cavernosum, thereby increasing the flow of blood into the sinusoidal spaces of the corpora cavernosa. The resulting corporeal engorgement produces veno-occlusion by compression of the subtunical emissary veins against the tunica albuginea (Lue 2000). Nitric oxide is an important mediator of noncholinergic nonadrenergic corpus cavernosum relaxation. In vivo studies of isolated corpus cavernosum tissue from diabetic men have demonstrated functional impairment in autonomic and endothelial dependent nitricergic relaxation of corpus cavernosum smooth muscle (Saenz de Tejada et al 1989).

Pharmacotherapy of erectile dysfunction. Oral therapy with sildenafil, the selective phosphodiesterase 5 inhibitor, is now the first line therapy for male erectile dysfunction (Rendell et al 1999). Not all patients with autonomic failure respond to this medication. The medication is contraindicated in patients treated with nitrates and agents that compete with or inhibit the cytochrome P-450 system. Angina, hypertension requiring treatment with multiple medications, and congestive heart failure are also contraindications (Kloner and Zusman 1999). Some phosphodiesterase 5 inhibitors, ie, vardenafil, tadalafil, and avanafil, are approved by the United States FDA for the treatment of erectile dysfunction. The dopamine (D1- and D2-receptor) agonist, apomorphine, administered sublingually is approved for the treatment of erectile dysfunction in the European Union. Apomorphine is approved by the United States FDA for the treatment of Parkinson disease.

Other pharmacological therapies include the injection of vasoactive substances such as papaverine, phentolamine and prostaglandin E1 into the corpus cavernosum, and transurethral delivery of vasoactive agents (Virag 1982; Zorgniotti and LeFleur 1985; Stackl et al 1988; Zentgraf et al 1988; Linet and Ogrinc 1996). The use of mechanical devices such as the vacuum erection device or constricting rings (Witherington 1988) and penile prosthetic implants may be used if these therapies fail or are not tolerated by the patient.

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**References especially recommended by the author or editor for general reading.

**Former authors**

Roy Freeman MD (original author)

**Profile**

**Age range of presentation**

- 0-01 month
- 01-23 months
- 02-05 years
- 06-12 years
- 13-18 years
- 19-44 years
- 45-64 years
65+ years

**Sex preponderance**

male=female

**Family history**

family history may be obtained for hereditary autonomic neuropathy

**Heredity**

heredity may be a factor

**Population groups selectively affected**

none selectively affected

**Occupation groups selectively affected**

none selectively affected

**Associated disorders**

Bladder hypomotility
Bowel hypomotility
Diabetic gastroparesis
Erectile dysfunction
Orthostatic hypotension
Postural orthostatic tachycardia syndrome.

**Other topics to consider**

Acute autonomic neuropathies
Chronic autonomic neuropathies
Diabetic neuropathies
Nutrition-related neuropathies