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Current Treatments in Familial Dysautonomia

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Abstract

Introduction—Familial dysautonomia (FD) is a rare hereditary sensory and autonomic neuropathy (type III). The disease is caused by a point mutation in the IKBKAP gene that affects the splicing of the elongator-1 protein (also known as IKAP). Patients have dramatic blood pressure instability due to baroreflex failure, chronic kidney disease, and impaired swallowing leading to recurrent aspiration pneumonia, which results in chronic lung disease. Diminished pain and temperature perception results in neuropathic joints and thermal injuries. Impaired proprioception leads to gait ataxia. Optic neuropathy and corneal opacities lead to progressive visual loss.

Areas covered—This article reviews current therapeutic strategies for the symptomatic treatment of FD, as well as the potential of new gene modifying agents.

Expert opinion—Therapeutic focus on FD is centered on reducing the catecholamine surges caused by baroreflex failure. Managing neurogenic dysphagia with effective protection of the airway passages and prompt treatment of aspiration pneumonias is necessary to prevent respiratory failure. Sedative medications should be used cautiously due to risk of respiratory depression. Non-invasive ventilation during sleep effectively manages apneas and prevents hypercapnia. Clinical trials of compounds that increase levels of IKAP (ELP-1) are underway and will determine whether they can reverse or slow disease progression.

Keywords

Hereditary Autonomic Neuropathy; Nausea; Hypertensive surges; Splicing modification therapy; Future directions

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1. Introduction

Familial dysautonomia (FD, OMIM# 223900) is a rare, autosomal recessive disease first described in 1949 by Riley and Day in children of European Jewish ancestry.¹ Carrier testing became available in 1993.² Over 99% of affected patients are homozygous for the common point mutation (6T>C change) in the gene encoding for the elongator-1 protein (ELP-1), known also as I-k B kinase-associated protein (IKAP).³⁻⁵ IKAP (ELP-1) is expressed in most cells throughout the body, including neurons in the central nervous system (CNS).⁶ The defect is in pre-mRNA splicing that skips exon 20 and transcribes a truncated unstable protein.^{3, 7} For unknown reasons, the splicing error is variable among tissues. While neuronal tissue makes almost no normal protein, other cells like fibroblasts express variable levels of correctly spliced IKAP (ELP1) mRNA and normal protein.^{3, 7}

The function of IKAP (ELP1) is not well understood. It has been implicated in the migration, survival, and myelination of neurons during development and plays a role in elongational transcription as a regulator of downstream gene expression.⁸ In humans, the deficiency of IKAP (ELP-1) during embryogenesis affects the development of primary sensory (i.e., afferent) neurons carrying information to the CNS. In addition to the impaired development of sensory neurons with cell bodies in the dorsal root ganglia (DRG), sensory neurons in the cranial nerves are also affected. On the other hand, efferent (motor) neurons are mostly spared.

FD is expressed from birth. It has full penetrance, but phenotypic severity varies. The neurologic abnormalities secondarily affect multiple systems (Figure 1). Gait ataxia (i.e., imbalance) and visual loss due to optic neuropathy worsen over time, suggesting that there is also a component of progressive neurological decline. Gastrostomy and fundoplication surgery at an early age became common in the 1970's.⁹ While these interventions facilitated patient management, the treatments are far from ideal. Although there is no cure for FD, quality of life can be enhanced through targeted symptomatic treatments. Treatment decisions were made empirically in the past, and much of our understanding of the outcomes of therapies comes from retrospective data reviews. Controlled clinical trials in FD are possible, although difficult, as the cases are rare and the population is fragile.¹⁰ Table 1 summarizes the current pharmacologic treatments for FD.

2. Cardiovascular treatments

The cardiovascular phenotype of FD is characterized by unstable blood pressure as a direct result of afferent baroreflex failure (Figure 2A).¹¹ FD impairs the development of afferent (sensory) neurons that relay information from the peripheral baroreceptors through cranial nerves IX and X to the brainstem. Therefore, the normal baroreflex buffering that prevents blood pressure from rising and falling excessively is absent.

Patients with FD have both hypertension and hypotension. Management is challenging as aggressive treatment of either one exacerbates the other (Figure 3B). Over time, this excessive blood pressure variability is associated with target organ damage, and treatment is geared towards lessening overall blood pressure variability (Figure 3C).

2.1. Hypertension

Loss of feedback from the arterial baroreceptors (i.e., afferent baroreflex failure) leads to the inability to restrain sympathetic outflow to the periphery. Cognitive/emotional and physical stressors trigger unopposed catecholamine release that raises blood pressure and heart rate in parallel (Figure 2C). The hypertensive peaks are frequently associated with nausea and retching. Fixed hypertension can also develop chronically secondary to advancing renal failure.

Appropriate management of hypertension depends on the underlying cause.

Transient hypertensive surges occur with everyday activities. They are common when awakening from sleep, while eating, or when a patient is anxious, excited, or frustrated. Hypertensive surges are present from infancy and are accompanied by erythematous (reddish) blotching of the skin and diaphoresis (excessive sweating).¹² As a first line of treatment, relaxation and/or distraction are frequently effective in managing emotionally-induced episodes. Standing or walking can lower blood pressure as this causes blood to pool in the lower extremities, as well as a decline in stroke volume and cardiac output.

Hypertensive vomiting attacks are a characteristic feature of FD. These attacks occur when stimuli that increase sympathetic outflow are not abated and catecholamine release continues unrestrained. In addition to the secretion of epinephrine and norepinephrine, plasma dopamine also spills over into the circulation (Figure 2C). It is the increase in plasma dopamine that is believed to activate D₂ and D₃ receptors in the chemoreceptor trigger zone of the area postrema outside of the blood-brain barrier and cause vomiting (or retching in patients with fundoplication, see below).¹³ These so-called “dysautonomic crises” can last several days. Common triggers include emotions, infection/illness, or surgery, as well as other situations such as constipation or bladder distension that may not be immediately apparent. Attacks are sometimes unpredictable and without obvious cause. Infection should be suspected and appropriately investigated.

Standard antiemetic (anti-vomiting) medications (e.g., serotonin 5-HT₃ receptor antagonists) are seldom effective. Acute treatment with benzodiazepines can be quite effective in reducing retching/vomiting, although controlled studies are lacking.¹⁴ Unfortunately, benzodiazepines markedly suppress ventilatory drive in patients with FD. Therefore, non-invasive ventilation is recommended as a precaution following the administration of benzodiazepines. Benzodiazepines can be administered through the gastrostomy tube or rectally. Because of the risk of respiratory arrest, intravenous administration should only be done in the intensive care unit (ICU) with continuous monitoring. Tolerance and dependency occur quickly.

Although there have been no controlled trials, the centrally acting α_2 -adrenergic agonist clonidine is frequently used to restrain sympathetic activity during the hypertensive vomiting attacks.¹⁵ Fatigue, sedation, and hypotension are common complications. The transdermal clonidine patch (0.1–0.3 mg/24h) provides stable blood levels and is preferable to oral dosages, which are associated with rebound hypertension. Slow tapering is recommended when discontinuing clonidine treatment.

We have used intravenous dexmedetomidine successfully in a few FD patients with severe hyperadrenergic dysautonomic crises who were admitted to the ICU. This selective agonist acts on α_2 adrenoreceptors in the brain and spinal cord to inhibit sympathetic outflow, resulting in hypotension, bradycardia, sedation, analgesia, reduced salivation, and decreased bowel motility.¹⁶

Hypertensive vomiting attacks are sometimes associated with excessive secretion of vasopressin, anti-diuresis, water retention, and hyponatremia.¹⁷ Hyponatremic seizures have occurred in a number of cases. Serum sodium should be corrected slowly.¹⁸ Since patients do not regulate water intake through thirst, they should be cautioned to avoid excessive free water intake through the gastrostomy tube to avoid water intoxication.

A new approach to treatment is the use of carbidopa, a reversible dopa-decarboxylase inhibitor. A recent double-blind, randomized, placebo-controlled clinical trial provided level II-b evidence that treatment with carbidopa can reduce the frequency and severity of hypertensive vomiting attacks (Figure 4A and Figure 4B). Carbidopa blocks dopamine synthesis and was administered at a dose of 200 mg three times daily.¹⁰ Since it does not cross the blood-brain barrier, its effects are confined to the periphery. Unlike previous treatment options, carbidopa is not associated with sedation or respiratory depression, making it suitable as a long-term pharmacotherapy to prevent the vomiting attacks. The downstream effects of carbidopa on norepinephrine production may also be useful to dampen hypertensive surges and lessen overall blood pressure variability (Figure 2B and Figure 2C).

Sustained supine hypertension is usually present in FD patients with advanced chronic kidney disease. Recent work from our laboratory has shown that brachial-artery reactivity, an index of nitric oxide-mediated endothelial function, is significantly reduced in FD patients with renal insufficiency.¹⁹ This finding suggests that impaired nitric oxide-mediated vasodilation plays a role in the chronic hypertension of renal disease in FD. The synthetic mineralocorticoid fludrocortisone exacerbates supine hypertension (Figure 3A and 3B).

Current guidelines for the treatment of hypertension in patients with chronic kidney disease in the general population recommend starting with an angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker, or calcium channel blocker.²⁰ Prospective studies are underway to determine the impact of the different anti-hypertensive drug classes on renal outcomes in patients with FD. ACE-inhibitors were associated with hyperkalemia in a few FD patients and had to be discontinued. Although a thiazide-type diuretic is also recommended,²⁰ we avoid diuretics in patients with FD because decreasing intravascular volume worsens orthostatic hypotension. Frequently, more than one antihypertensive agent is required.

Nocturia is often an indication of hypertension during the night and can be detected on ambulatory blood pressure monitoring. Sleeping with the head of the bed raised (20-40°) lowers blood pressure, reduces nocturnal pressure-diuresis, and raises intravascular volume in the morning. This simple intervention is an effective way to lessen symptoms of orthostatic hypotension in the morning.²¹ In some cases, anti-hypertensive agents at night

may still be necessary. In patients taking anti-hypertensive medications in the evening, nocturnal blood pressure monitoring should be performed to screen for excessive blood pressure dipping during sleep, which may have deleterious effects on the kidney.²²

2.2. Tachycardia

Since hypertension and tachycardia go hand-in-hand in FD, agents that restrain or block sympathetic outflow to the vasculature also lessen tachycardia. Beta-blockade with propranolol can be useful in some patients, especially as this agent crosses the blood brain barrier and has a mild anxiolytic effect. Careful monitoring of serum potassium levels is necessary when using beta-blockers. Intravenous labetalol has been used in the ICU setting. Its effects are usually moderate.

2.3. Orthostatic hypotension

In patients with FD, the normal reflex increase in sympathetic outflow on standing is absent due to the lack of sensory feedback from arterial baroreceptors.¹¹ This failure to increase sympathetic activity results in orthostatic hypotension, which is exacerbated by exercise and warm environments. Syncope is surprisingly infrequent, however, and usually indicates volume depletion, anemia, or hypoxia. Therefore, in FD patients experiencing syncope, gastrointestinal bleeding, dehydration, or worsening hypoxia (e.g., mucus plug, pneumonia) should be suspected and treated first. Breath-holding spells should be considered in the differential diagnosis of syncope, especially in younger children. Non-pharmacological interventions to lessen orthostatic hypotension should be implemented before drug therapy.

Non-pharmacological strategies—Patients should be instructed to avoid potential triggers such as standing immobile for a long time and standing quickly after long periods sitting. Physical counter-maneuvers to raise venous return and increase blood pressure are effective. Typical maneuvers are leg crossing, wiggling the toes, muscle tensing, and abdominal compression, which have been shown to lessen orthostatic hypotension.²³ More recently, chewing gum was discovered to induce a marked pressor response in these patients.²⁴ A physical therapy program with emphasis on increasing muscle strength in the extremities is helpful. Sleeping with the head of the bed elevated (see above) raises intravascular volume and blood pressure in the morning. Adequate hydration and liberal salt intake are essential, although the immediate osmopressor response triggered by water loading appears to be absent in FD.²⁵

Pharmacological agents—The α -1 adrenergic agonist midodrine (5–20 mg) raises blood pressure for ~3 hours.²⁶ Rather than at a fixed schedule, midodrine should be administered depending on daily activities. Since the peak effect is around 1 hour after oral administration, midodrine should be taken ~45 minutes before physical activity, so that the pressor effect coincides with exercise-induced hypotension. Patients should be instructed to avoid lying down 3 hours post-dose and to avoid midodrine when inactive or during a hypertensive crisis.²⁷

As a cautionary note, treatment of orthostatic hypotension with high doses of fludrocortisone (>0.2 mg/day) was shown to accelerate the progression of renal damage in patients with FD.

It is not known whether this is a direct fibrotic effect of mineralocorticoid receptor activation in the kidney or a result of the supine hypertension produced by fludrocortisone. Whether fludrocortisone also accelerates the progression of renal disease in other autonomic disorders is not known. In addition, the associated fludrocortisone-induced metabolic alkalosis causes respiratory depression²⁸ and worsening of hypercapnia. Dosages of fludrocortisone should be tapered slowly, with careful monitoring of serum potassium levels, as hyperkalemia can occur during mineralocorticoid withdrawal.

Anemia of chronic disease occurs frequently in patients with FD. Erythropoietin treatment is emerging as a useful adjunct therapy to manage orthostatic hypotension. Raising red blood cell mass provides increased oxygen carrying capacity and reduces circulating nitric oxide levels, thereby raising blood pressure.²⁹ Patients with FD usually respond well, but close monitoring to avoid polycythemia or sustained hypertension is required.

3. Gastrointestinal treatments

In addition to hypertensive vomiting attacks (discussed above), abnormal gastrointestinal motility and feeding difficulties are lifelong problems for patients with FD.^{30, 31} Aspiration pneumonia remains a leading cause of death.³² FD patients receiving long-term treatment for pneumonia are prone to develop *Clostridium difficile* (*C. diff*) infection. Symptoms include watery diarrhea with or without fever. Treatment of *C. diff* in FD is similar to that in the general population, comprising metronidazole or vancomycin.³³

3.1. Sucking disorders and neurogenic dysphagia

Poor initiation of sucking and dysphagia (i.e., difficulty swallowing) are usually the presenting signs of FD in a newborn.¹² Impaired brainstem reflexes underlie these abnormalities.³⁴ Pharyngeal pooling and aspiration usually occur in the nursery.¹² A videofluorographic swallow study (modified barium swallow study) allows for the visualization of bolus flow throughout the upper aero-digestive tract in real time and is used to examine the presence and timing of aspiration (i.e., entry of ingested material into the airways).³¹ Thickened formula and nasogastric feeding may be required to manage caloric intake in infants. Feeding aversion and failure to thrive are managed with percutaneous endoscopic gastrostomy (PEG) placement.³⁵ Neurogenic dysphagia persists throughout life, and eating by mouth can become a challenge.

3.2. Sialorrhea

Dysphagia and sialorrhea (i.e., excessive production of saliva) contribute to drooling, a common feature in patients with FD.³⁶ Drooling worsens during a hypertensive vomiting attack, and aspiration of saliva can cause pneumonia.³⁷ Anticholinergic drugs, like glycopyrrolate, block parasympathetic activity and diminish salivary production. Side effects include decreased lacrimation with worsening of dry eyes, as well as pupillary dilatation, inhibition of the accommodation reflex, and blurred vision.³⁸ Surgical interventions, including ligation, transposition, reduction, or removal of the salivary glands have been performed,^{37,38} but there is not enough available data to determine how effectively they reduce saliva production. A recent report from a small case series of patients

with FD describes the safety and effectiveness of botulinum toxin injected into the major salivary glands as a treatment for drooling in FD.^{37, 39}

3.3. Gastroesophageal reflux

Gastroesophageal reflux occurs in 75% of FD patients.³² Abnormalities in esophageal peristalsis and abnormal control of the lower esophageal sphincter may both contribute to driving the gastric contents back into the esophagus in patients with FD.³¹ Regurgitated stomach contents can be vomited or aspirated into the lungs, resulting in chemical pneumonitis (i.e., inflammation of the respiratory tract).⁴⁰ Thickened fluids and smaller more frequent meals are the first steps in management.⁴¹ Histamine H₂ receptor antagonists (ranitidine/cimetidine/nizatidine) can be used acutely to reduce gastric acidity, but tachyphylaxis soon occurs.⁴² Proton pump inhibitors (omeprazole/lansoprazole/rabeprazole) have been used in patients above the age of 1 year.⁴² Magnesium hydroxide, aluminium hydroxide, alginate, or sucralfate are used by some patients. Unfortunately, the long-term consequences of gastric acid suppression in this population are unknown.

The prokinetic dopamine receptor blocker metoclopramide can accelerate gastric emptying and improve GER. Persistent tardive dyskinesia (i.e., involuntary movements) and hyperprolactinemia with galactorrhea (i.e., milky nipple discharge) make it unsuitable as a chronic treatment.⁴² The D₂-receptor antagonist domperidone has the advantage of not significantly crossing the blood-brain barrier.⁴³ In addition to its prokinetic effects, its antiemetic effects can be useful. Domperidone is not available in the US, but is used in Europe, Canada, and Central and South America. Careful monitoring of the electrocardiographic QT interval is recommended as it may be prolonged with domperidone treatment.

Although not the focus of this pharmacotherapy review, fundoplication surgery has been performed in 72% of patients with FD in the US.^{35, 44} The impact of the fundoplication wrap on the natural history of these patients compared with that of untreated patients is still unclear. GER can reoccur after the fundoplication,³² and up to 12% of patients who underwent the procedure required a second surgery. Esophageal dilatation and achalasia (i.e., abnormal esophageal peristalsis) are increasingly recognized complications after fundoplication surgery.^{45, 46}

3.4. Retching and vomiting

Hypertensive vomiting crises (discussed above) are a cardinal feature of the disease and occur because of unrestrained catecholamine release.¹⁰ Strategies that blunt catecholamine synthesis peripherally are effective.¹¹

3.5. Cholelithiasis

Biliary function is not well understood in FD. Gallbladder volume before eating is smaller, but contraction after fat-rich meals is reportedly normal.⁴⁷ Cholelithiasis (i.e., gallbladder stones) is a relatively frequent complication in FD and usually requires surgical management.

3.6. Necrotizing enterocolitis

Necrotizing enterocolitis (i.e., necrosis of the bowel) can occur in the neonate, with severe hemorrhagic necrosis in the mucosa and submucosal layers.⁴⁸ As in the general population, the incidence of necrotizing enterocolitis in FD patients is more common in low birth weight, premature babies.⁴⁹ Two cases of intestinal ischemic necrosis in older FD children have been reported.^{50, 51} The presenting features of necrotizing enterocolitis include abdominal distension, feeding intolerance, bloody stools, and intestinal pneumatosis (i.e., air within the intestinal layers). Its causes in FD are unknown.^{48, 52} Management requires intensive supportive care with the administration of intravenous fluids and pressor agents. Anti-cytokine agents and corticosteroids may be used to suppress inflammation. Urgent surgical resection of the affected colon may be required.⁵³

4. Respiratory treatments

Respiratory complications are almost always present in FD patients. Failure to receive input from the peripheral chemoreceptors, which is normally carried to the CNS via the IX and X cranial nerves, results in markedly blunted ventilatory responses to hypoxia.⁵⁴ Ventilatory responses to hypercapnia are reduced, but still present.⁵⁴ Moreover, there is no compensatory increase in sympathetic outflow in response to hypoxia; instead, FD patients exhibit bradycardia and hypotension.⁵⁴ Intrinsic lung disease develops over time as a consequence of recurrent aspirations. Bronchiectasis (i.e., permanent enlargement of bronchi) and atelectasis (i.e., collapse or closure of bronchi) are common. Neuromuscular impairment and spinal deformities result in severe restrictive lung disease, with forced vital capacity (FVC, i.e., maximum amount of air expelled from the lungs after a maximum inspiration) around 54% of expected (range: 30–79%). Impaired autonomic control of the airway is also likely, and may explain the obstructive component.

In a cross-sectional series of 91 FD patients, arterial blood gases revealed an average PaCO₂ of 43 mmHg (range: 34–57 mmHg; normal value: 35–45) and average PaO₂ of 87 (range: 46–100 mmHg; normal value: >80) with a mean pH of 7.41±0.03 (range: 7.32–7.51; normal value: 7.35–7.45). These results highlight the fragile respiratory equilibrium in these patients, which is easily disrupted by mild insults (e.g., hypoxia of high altitude, seasonal asthma).

4.1. Respiratory infections

In one of the earliest description of the disease, Riley found that 74% of FD patients had a history of pulmonary infections.⁵⁵ Aspiration pneumonias are a recurrent problem caused by neurogenic dysphagia, GER, or vomiting. Damage to the lungs occurs early and (many times) irreversibly in infancy and childhood when neurogenic dysphagia is severe and caloric intake is based on thin liquids, which are more likely to be aspirated into the lung.

Aggressive treatment of bacterial pneumonia is essential. Pneumonia is often accompanied by hypertensive vomiting crisis with fever, cough, congestion, and wheezing. Presentation may vary, however, and signs can be subtle or absent. Tachypnea (i.e., increased respiratory rate) is rarely present because of the blunted hypoxic ventilatory drive.⁵⁶ Low oxygen saturations usually indicate the presence of an acute respiratory infection. CO₂ retention

(hypercapnia) requires assisted ventilation. Sputum cultures may be confusing because the offending organisms may not be the usual ones. *E. coli* and other gastric flora are common etiological agents and, until the causative microorganism is identified, broad-spectrum antibiotic therapy covering enterobacteriaceae (e.g., levofloxacin) should be initiated.

Patients with FD are also at increased risk for viral respiratory infections and, in many cases, there is concomitant bacterial infection. Cases of influenza have been fatal. If influenza is suspected, a rapid influenza antigen test (nasal swab) should be performed and, if the result is positive, treatment with oseltamivir should be initiated.⁵⁷ As patients with FD are at high risk for complications from influenza, prophylactic treatment with oseltamivir is indicated if close relatives/care providers have a confirmed influenza infection.

4.2. Chronic respiratory disease

In addition to recurrent aspiration bronchopneumonias and blunted ventilatory drive, pulmonary function tests almost always show a pattern of restrictive lung disease. Neuromuscular abnormalities impair the strength and coordination of respiratory muscles, preventing efficient chest expansion and cough clearance. Abnormal spinal curvature further decreases chest wall compliance.⁴⁵

A comprehensive clinical evaluation is required to implement appropriate long-term management. Standard work-up should include spirometry (achievable from age 6 years onwards), arterial blood gases, polysomnography, and a swallow study. If reversible bronchoconstriction is documented, bronchodilator therapy with beta-2-agonist or anticholinergic agents is frequently used and appears safe; however, no controlled trials have been performed. Oropharyngeal cultures may not reliably predict the presence of bacterial pathogens in the lower airways. Bronchoscopy may be necessary to visualize the airways and obtain lower airway specimens, particularly in children who are unable to expectorate. Chest physiotherapy geared toward airway clearance is essential for the management of chronic respiratory disease in patients with FD.

Standard chest physiotherapy consists of postural drainage in the head-down position and manual techniques such as percussion (chest clapping) and vibration (application of rapid extra thoracic force at the beginning of expiration, followed by oscillatory compressions until expiration is complete). Care should be taken when performing these techniques in infants to avoid atelectasis, as the chest wall is very compliant and the closing volume of the lung is high.

High-frequency chest wall oscillation (HFCWO) can be provided by intermittent compression of the chest wall using an inflatable vest or cuirass over the thorax. Vibration of the chest wall produces oscillatory airflow, which, in turn, promotes mobilization of secretions from the distal airways toward the mouth.⁵⁸ HFCWO decreased the number hospitalizations, physician visits, and antibiotic use in a 1-year study of patients with FD. Regular use of the vest was associated with improved oxygen saturation.⁵⁹ Nebulized normal saline may be considered in children who have continued tenacious secretions. When using any sputum-mobilizing technique, appropriate emergency equipment (e.g., a

resuscitation bag and suction equipment) should be available as large mucus plugs can become lodged in the central airways, causing airway obstruction.⁶⁰

Cough-augmentation is a key component of effective airway clearance. This can be achieved by practicing efficient deep breathing and coughing. Mechanical insufflation/exsufflation methods were shown to be useful in patients with other types of neuromuscular respiratory disease.⁶¹

Incentive spirometry devices designed to mimic natural sighing or yawning by encouraging the patient to take long, slow, deep breaths are useful tools. Regular use increases inspiratory volumes and improves inspiratory muscle performance. Visual or other positive feedback during inhalation is useful to sustain the inflation for a minimum of 3 seconds. This device is particularly helpful in the postoperative period.

4.3. Sleep-disordered breathing

Sudden death during sleep is the leading cause of death in FD patients.⁶² Sleep in healthy individuals is associated with reduced tone in the upper airway and intercostal muscles, especially during the rapid eye movement (REM) stage. In patients with FD, these changes can result in sleep-related hypoventilation and/or obstructive sleep apnea (OSA), producing severe hypoxemia and hypercapnia.^{63, 64} The arousal response to hypoxemia and hypercapnia is lacking in patients with FD, and hypotension and bradycardia develop in response to hypoxia.⁵⁶ Screening for sleep disordered breathing with polysomnography is recommended for all patients with FD, regardless of symptoms. If sleep-disordered breathing is confirmed, treatment with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) must be initiated. Medications that depress respiration (e.g., opiates, benzodiazepines, fludrocortisone) should be avoided. Supplemental oxygen further depresses respiration, and extreme caution should be exercised when it is used alone without assisted ventilation.

4.4. Daytime respiratory failure

Daytime respiratory failure and hypercapnia tend to develop slowly and are usually preceded by sleep-related hypoventilation. Daytime hypercapnia is usually an indication of progression of respiratory muscle weakness and/or reduced lung compliance and carries a poor prognosis. Nocturnal non-invasive assisted ventilation with CPAP/BiPAP usually improves hypercapnia during the day and night. Environmental situations associated with hypobaric hypoxia (e.g., aircraft flight or ascent to high altitude) pose a potential risk. In these circumstances, FD patients should receive continuous supplemental oxygen (2-3 liters/min) administered via nasal cannula.

5. Renal and urologic treatments

There is an increased incidence of renal patterning defects in FD, suggesting that IKAP (ELP-1) deficiency may also affect kidney development.²⁸ Chronic renal failure is a frequent problem in patients with FD. Paroxysmal hypertension occurs from birth and is associated with a faster progression of renal damage (Figure 3A), a finding that underscores the need for adequate control of blood pressure. Creatinine may not accurately reflect

glomerular filtration rate as muscle mass is often abnormally low in these patients. End-stage renal disease may require dialysis. A few renal transplants have been performed.⁶⁵

Aggressive treatment of the hypotension with fludrocortisone (>0.2 mg/day) hastened the progression of renal failure in patients with FD (Figure 3B).²⁸ Prospective studies of potential nephro-protective strategies focused on lessening blood pressure variability and treating sustained hypertension are ongoing.

Renal tubular acidosis occurs more frequently in patients with FD. Treatment with bicarbonate is often required. Hyperkalemia is also common and can be managed with a low potassium diet or treatment with a low dose of fludrocortisone. These electrolyte imbalances are not always explained by the degree of renal insufficiency.

More than 80% of female patients with FD report stress incontinence.⁶⁶ Nighttime bladder control is usually achieved at a later age than in normal children. Treatment with desmopressin should be avoided due to the propensity for hyponatremia.⁶⁷ Pressure natriuresis and nocturia may be the result of supine hypertension.

6. Ophthalmological treatments

Visual impairment is almost always present in FD patients. Optic neuropathy is already noticeable in early childhood (from age 7 years onwards) and progressively worsens with age.^{68, 69} Corneal opacities, neurotrophic keratopathy (i.e., corneal damage as a result of poor tear secretion and corneal hypoesthesia), myopia (i.e., short sightedness), eye movement abnormalities, and strabismus (i.e., misalignment of the eyes) are additional causes of low visual acuity, color vision defects, and visual field loss that can progress to legal blindness.⁶⁹⁻⁷²

6.1. Dry eye

Decreased secretion of basal, reflex, and emotional tears is one of the diagnostic features of FD. Therapeutic approaches focus on maintaining corneal moisture to avoid dry eye complications, including recurrent corneal abrasions, ulcers, and permanent opacities.⁷³ Treatments include preservative-free artificial tears (every 2-3 hours), liquid gels (every 4-6 hours), and ointments (e.g., carboxymethyl cellulose, glycerin, mineral oil, or white petrolatum at bedtime or every 8-12 hours). Temporary or permanent closure of the tear ducts to decrease tear evaporation has been performed.⁷⁴ Lagophthalmos (i.e., improper eye closure) is common and may result in corneal abrasions during non-invasive ventilation or while wearing oxygen masks. Moisture chamber goggles may be necessary during sleep. Temporary use of bandage contact lenses to protect the cornea may be required. Moderate to severe complications of neurotrophic keratopathy can be managed with scleral support contact lenses (Prosthetic Replacement of the Ocular Surface Ecosystem, PROSE).^{75, 76} PROSE lenses should be removed after 12 hours. Patients often require assistance to insert or remove the lenses due to poor dexterity. In exceptional cases, poorly healing ulcerations may require temporary complete surgical closure of the eyelids.

6.2. Eye infections and corneal ulcers

“Red eye” should be immediately evaluated to rule out infections such as chronic blepharitis, bacterial conjunctivitis, and fungal keratitis. Chronic blepharitis is frequent and requires treatment with combined topical antibiotic/corticosteroid ointment (erythromycin, sulfacetamide, and prednisolone). Unhealed abrasions can lead to corneal ulcers.⁷⁴ In this case, all topical eye drugs should be withdrawn and only preservative-free artificial tears used. Close follow-up is necessary to evaluate the need for antibiotic therapy. Severe corneal opacities occur in around 30% of FD patients. Some cases may require corneal transplant, but success rates are low due to poor wound healing and epithelial defects.⁷⁷

6.3. Eye movement abnormalities and strabismus

Saccades (i.e., fast movements of the eyes) are abnormal in 75% of FD patients and are followed by several corrective re-fixation movements. Pursuit movements are usually interrupted by saccadic intrusions (67%), and optokinetic responses (i.e., eye movements when following moving objects) are slowed.^{69, 70} Strabismus is almost always present (93%), and early surgical correction may help prevent blindness.

6.4. Optic neuropathy and retinopathy

Optic neuropathy, preferentially affecting the P ganglion cells of the central retina, is a characteristic and progressive feature of the disease that accounts for visual loss over time.^{69, 70} There are currently no treatments, but retinal ganglion cells may be accessible by intravitreal injections and amenable to future therapies.

7. Orthopedic and muscular treatments

7.1. Spinal deformities

By the age of 10 years, 52% of patients with FD have scoliosis (sideway curvature of the spine) and 21% have kyphosis (round/hunchback).⁷⁸ By the age of 20 years, 83% of FD patients have spinal deformities.⁷⁸ Abnormal curvature of the spine displaces the thoracic cage and diaphragm. The resulting asymmetric inspiration and decreased chest wall compliance limits vital capacity. Physiological dead space is increased, leading to retention of CO₂ (see above). Scoliosis can also distort the center of gravity, triggering compensatory pelvic or neck distortion.

Bracing has been used in FD patients with spinal deformities, but with little success.⁷⁸ Because rigid braces can cause inadvertent pressure ulcers, the skin should be inspected daily. Braces can also inhibit respiratory excursion. Non-rigid dynamic braces are better tolerated, but their effectiveness in halting spinal curvature in FD is unknown. Corrective surgery may be required. The optimal timing of scoliosis surgery in children with FD is not clearly defined. Early surgery with flexible and relatively mild curves and good lung function (vital capacity over 50% predicted) is less taxing to the patient and surgeon.⁷⁹ Whether surgery leads to an improvement in vital capacity or slows the rate of decline in respiratory function is unknown.

7.2. Other orthopedic problems, including osteopenia

Up to 60% of patients experience at least one fracture during their lifetime,⁸⁰ with a higher incidence of femoral and neck fractures than in normal subjects. Insensitivity to pain complicates bone fracture detection. Patients with FD exhibit decreased cervical motion.⁸¹ Inadvertent trauma to joints increases the risk for neuropathic arthropathy (Charcot joints are present in 11% of patients, particularly at the knee)⁸⁰ and aseptic necrosis.⁸² Other bone abnormalities, such as rotational misalignment (external tibial torsion), valgus feet, hallux valgus, and leg-length discrepancies may also occur.⁸⁰ A significantly lower bone mineral density has been documented.⁸³ The cause of osteopenia in FD is unclear, but risk factors include reduced body mass index, reduced physical activity, and poor nutrition; there is evidence of vitamin D deficiency in 9% of patients with FD.⁶² Whether treatment with bisphosphonates or vitamin D supplementation improves bone density and lessens fracture rates in FD patients is not known.

7.3. Rhabdomyolysis

Patients with FD are at increased risk for rhabdomyolysis (i.e., breakdown of striatal muscle tissue). This may be due to prolonged immobilization, a primary muscle abnormality, or both.⁸⁴ Rhabdomyolysis can occur painlessly or with diffuse discomfort and weakness. Diagnosis is made by detecting high serum creatinine kinase (CK) levels (> 1,000 U). Because of the risk of renal failure, patients with rhabdomyolysis should receive intravenous hydration. As a general rule, normal saline should be initially given at a rate of 1.5 liters/hour. Urine output should be maintained at 300 ml/h until the CK level decreases to 1,000 U or below. Preventative measures include frequent postural changes (particularly during prolonged recumbency, e.g., during dysautonomic crises), treatment of fever, and adequate hydration.

8. Growth

Although well-balanced dietary regimens and the availability of the PEG tube have improved nutritional status,⁶² patients with FD often fall severely below their projected height. In an open-label study, treatment with growth hormone resulted in growth velocity that exceeded pre-treatment rates in 12 out of 13 FD patient after 6 months of treatment; 10 patients achieved an annualized growth rate >7 cm/year. Six of nine patients treated for more than one year grew >5 cm/year.⁸⁵ Spinal curvature tends to worsen at times of accelerated growth.

9. Neurological treatments

9.1. Seizures

Around 40% of FD patients will experience at least one seizure during their lifetime, usually associated with fever, breath-holding, or hyponatremia.⁸⁶ About 25% of FD patients have an “abnormal” electroencephalogram, but less than 10% have recurrent seizures.⁸⁷ The type and dosages of anti-epileptic drugs are the same as for other patients.⁸⁸

9.2. Gait ataxia

The gait of most FD patients is ataxic (i.e., uncoordinated and unbalanced). Patients adopt a wide stance (broad base), veer into walls, and can be remarkably unsteady on turning. Deprived of vision, they stagger or fall, (i.e., have a positive Romberg sign). Gait ataxia worsens over time. At least 50% of adult patients require assistance with walking. As deep tendon and H-reflexes are absent⁸⁹ and autopsy shows little evidence of cerebellar atrophy, the ataxia appears to be of sensory origin (i.e., proprioceptive). Indeed, muscle spindle afferents are functionally absent⁹⁰ and the decrease in proprioceptive accuracy is tightly correlated with the severity of gait ataxia.⁹¹ Cutaneous (tactile skin) afferent fibers appear to be intact, suggesting that strategies to increase sensory feedback from tensile strain in the skin may be useful in improving gait.

10. Psychiatric and behavioral treatments

10.1. Anxiety

Anxiety is the most common psychiatric problem in FD patients.⁹² Even mild anxiety results in marked hypertension and tachycardia that can progress to retching/vomiting. Treatment of anxiety in FD is fraught with difficulty. Benzodiazepines (e.g., diazepam) should be used sparingly as they depress both ventilatory drive and mood. Selective serotonin re-uptake inhibitors are sometimes effective, although controlled studies are lacking. Psychotherapy and behavioral techniques frequently help to manage anxiety, but require patience and a long term time commitment.

10.2. Obsessive-compulsive behavior

Skin or nail picking and trichotillomania (i.e., compulsive hair pulling) occur in ~10% of patients with FD. The inability to feel pain can result in deep wounds and scarring. Selective serotonin re-uptake inhibitors have been tried in some cases, but are not always effective. Cognitive behavioral therapy may be useful.

10.3. Other behavioral and learning difficulties

A variety of behavioral issues can arise in patients with FD.⁹² Careful consideration of family dynamics is important.⁹³ Boundaries and expectations are important in any FD patient and should be discussed with families. Behavioral therapy with a focus on the identification of inappropriate behavioral patterns and the positive reinforcement of desired behaviors is useful. Psychosis can occur. Caregivers frequently describe patients becoming withdrawn or agitated during a hypertensive-vomiting crisis. Drug-seeking behavior with addiction to benzodiazepines is often an overlooked psychiatric manifestation.

Cognitive function differs widely among patients with FD.⁹⁴ On one end of the spectrum are patients without verbal skills or bladder/bowel control; on the other end are patients who are able to graduate college and work full-time. Learning difficulties and poor concentration are both common. Stimulant drugs and norepinephrine reuptake inhibitors induce marked hypertension and should be avoided. Many patients require tailored educational programs. Parental counseling is essential to set realistic expectations.

11. Dermatological treatments

Due to decreased sensitivity to pain, special attention is necessary to prevent inadvertent decubitus ulcers, burns, cuts, ingrown toenails, or other minor injuries that may become infected. The management of these problems in patients with FD is not different from their management in patients without FD. Irritation around the gastrostomy site is common. Zinc oxide barrier cream is helpful.

12. Splicing modification therapy

Recently, two agents that can overcome the mis-splicing defect and increase the expression of wild-type (normal) IKAP (ELP-1) have become available. Clinical trials have demonstrated that IKAP (ELP-1) mRNA levels increase in the blood after oral administration of 6-furfurylaminopurine (kinetin 1000 – 1500 mg).⁹⁵ However, the tolerability of kinetin is hampered by nausea. Attempts are underway to optimize efficacy by altering the molecular structure of kinetin. Phosphatidylserine, a phospholipidic component of cell membranes, has been shown to raise IKAP (ELP-1) levels in cell lines and animal models of FD.^{96, 97} Initial studies of phosphatidylserine in a small number of FD patients have demonstrated an increase in IKAP (ELP-1) levels and have shown that it is safe and well tolerated.⁹⁸ Long-term trials are underway to determine whether raising IKAP (ELP-1) levels can rescue or delay the progressive worsening of neurological features like optic atrophy and gait ataxia. While kinetin increases the levels of correctly spliced IKAP transcripts, thus altering the ratio between exon 20 inclusion and skipping, phosphatidylserine appears to increase levels of transcription without altering the ratio. Because kinetin and phosphatidylserine have two different mechanism of action, it may be possible that using both agents together results in a more pronounced increase in IKAP.

13. Expert opinion

A well-organized nonprofit advocacy group of parents (<http://www.familialdysautonomia.org>), whose mission it is to support basic and clinical research into the disease, has created the infrastructure for a multidisciplinary research program.

Clinical research has unraveled the extent of afferent denervation and shown how severely affected the sensory pathways are, particularly those signaled by the cranial nerves.^{34, 70, 99} Understanding the autonomic phenotype as an afferent disorder has translated into better strategies to manage the blood pressure instability.²⁸ Treatment of anemia with erythropoietin has improved symptomatic orthostatic hypotension in a number of patients. Research data have identified blood pressure variability as a major culprit in target organ damage.²⁸ In keeping with this finding, therapeutic focus is on pharmacological strategies that reduce catecholamine surges without producing sedation or respiratory depression.¹⁰ Unfortunately, management of the hyperadrenergic crises is still suboptimal and many patients rely on sedative medications (diazepam and clonidine) with the risk of respiratory depression.

Respiratory failure remains a major handicap in FD. Aggressive management of respiratory complications is of paramount importance. Aspiration pneumonia and sudden death during

sleep are still among the top causes of mortality. Non-invasive ventilatory support at night has become the standard of care to manage sleep apneas and prevent the accumulation of CO₂. The impact of this on survival will be determined over the coming years. It seems likely that respiratory management in FD can benefit from the gains that have been made in other genetic diseases with severe respiratory compromise such as cystic fibrosis.¹⁰⁰

Hospitalization rates in patients with FD are still high. Frequent problems include electrolyte imbalances (hyponatremia, hyperkalemia), respiratory exacerbations (bronchiectasis, pneumonias), and muscle or bone injury (rhabdomyolysis, osteomyelitis). It has been suggested that reduced IKAP (ELP-1) levels may affect mitochondrial function and energy metabolism because, despite the availability of the PEG-tube to supplement caloric intake, weight gain and growth are still below target.

Clinical trials of kinetin, a supplement that can overcome the deficiency of IKAP (ELP-1) by modifying splicing^{95-97, 101} are underway. Pre-clinical studies to optimize kinetin are being conducted as part of the Blueprint Neurotherapeutics Network (1U01NS078025-01). The dietary supplement phosphatidylserine, once popular to enhance memory, has recently been shown to raise IKAP (ELP-1) levels in a small number of tested patients.⁹⁸

Since carrier and prenatal screening have become available, the number of new cases of FD has dwindled.¹⁰² However, two patients recently diagnosed with FD were of Mexican heritage and unaware of any Jewish ancestry, suggesting that the disease should be suspected in a wider population.

At present there is no available mouse model that faithfully reproduces both the genotype and the phenotype of FD.¹⁰³ The development of induced pluripotent stem cells grown from FD patients poses a unique opportunity to better understand the disease at a molecular level.¹⁰⁴ The possibility of using antisense oligonucleotides to rescue IKAP (ELP-1) during pre-mRNA splicing, a technique used in spinal muscular atrophy, is now also being considered as a therapeutic strategy in FD.¹⁰⁵ The prospect that any compound or molecular strategy could rescue the phenotype or slow the progressive course of the disease is an exciting frontier for translational research in FD. Research over the coming years should answer some of these unknowns.

14. Conclusions

In recent years, the life expectancy of patients with FD has increased substantially. Although classically a disorder of the sensory and autonomic neurons, FD also involves cardiovascular, respiratory, gastrointestinal, ophthalmological, osteomuscular, renal, and neuropsychiatric abnormalities. Phenotypic severity varies markedly among patients. Current treatments are limited to symptomatic and preventative care.

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Highlights

Familial dysautonomia is a rare, autosomal recessive disease caused by a point mutation in the gene encoding for elongator-1 protein (ELP-1, also known as IKAP).

Clinical hallmarks include reduced perception of pain and temperature, neurogenic dysphagia, excessive sweating, blood pressure instability, gait ataxia, and optic neuropathy.

A unique feature of FD is recurrent episodes of paroxysmal hypertension, tachycardia, excessive sweating, and vomiting. These episodes are frequently referred to as dysautonomic crises and occur because of unrestrained catecholamine release.

Current treatments are symptomatic and preventative. However, clinical trials of compounds that increase levels of IKAP (ELP-1), which may slow the progression of the disease, are currently underway.

Figure 1. Organs and systems affected in familial dysautonomia

The involvement of cardiovascular, gastrointestinal, respiratory, orthopedic, renal, and neurological systems contributes to morbidity and mortality.

Figure 2. Cardiovascular autonomic phenotype

(A) Shows representative ambulatory blood pressure monitoring in a patient with FD. Red arrow notes onset of hypertensive-vomiting crisis. (B) Shows exaggerated blood pressure variability in patients with FD (n=15) and age/sex matched healthy controls (n=12). (C) Shows cardiovascular autonomic changes during a dysautonomic crisis. Note, increase in blood pressure accompanied by release of dopamine and norepinephrine spillover into the circulation. BP, blood pressure; SD, standard deviation; SBP, systolic blood pressure; DA, dopamine; NE, norepinephrine. Modified with permission from *Norcliffe-Kaumann et al.*⁹⁹ and *Norcliffe-Kaumann et al.*¹³

Figure 3. Progression of renal disease

(A) Shows the cumulative probability of reaching the end point of a 50% decline in estimated glomerular filtration rate or progression to end-stage renal disease in patients stratified for the severity of hypertension in childhood. Note, patients with severe childhood hypertension (above AHA stage III) were more likely to progress to poor renal outcomes. (B) Shows change in eGFR over 5 years in adolescent patients treated empirically with fludrocortisone (mean dose 0.2 mg/day, n=20) vs. matched untreated FD patients (n=20). Of note, patients treated with high dose fludrocortisone had a faster decline in renal function.

Starting eGFR and severity of orthostatic hypotension were similar in both groups (data not shown). (C) Retrospective review showing more excessive blood pressure variability (24-h ambulatory monitoring) was associated with a faster rate of decline in eGFR overtime (13-year follow-up). Figure B reproduced with permission from *Norcliffe-Kaufmann et al.*²⁸

Figure 4. Effect of carbidopa on nausea, retching and dopamine output

(A) Shows significant reduction in nausea and retching outcomes in a double-blind randomized placebo controlled clinical trial of carbidopa in patients with FD. (B) Shows significant reduction in dopamine output on active carbidopa. PRO, patient reported outcome scale. Modified with permission from *Norcliffe-Kaufmann et al.*¹⁰

Table 1

Current pharmacologic therapies in familial dysautonomia

Drug	Mechanism of action	Dosage	Half-life	Most common adverse effects	Comments	Ref.
<i>Hypertensive, retching, and vomiting crises</i>						
Carbidopa	Dopa-decarboxylase inhibitor that reduces production of dopamine and norepinephrine.	<i>Oral or GT</i> : 200 mg three times/day (600 mg/day).	2 h.	Not described.	Reduces nausea and retching (Class IIb evidence). May decrease exaggerated blood pressure variability.	10
Clonidine	Centrally acting α_2 -adrenergic agonist that produces hypotensive and sedative effects.	<i>Oral or GT</i> : 0.10-0.5 (or 0.005 mg/kg) every 3-4 h. <i>Transdermal patch</i> : delivers a constant dose over 24 h (e.g., TTS-1 delivers 0.1 mg/day). Each patch lasts for 7 days.	12-16 h.	Dry mouth, drowsiness, constipation, sedation, severe hypotension, and blurred vision.	Use if systolic BP is > 160 mmHg or diastolic BP is > 100 mmHg. Frequent rebound hypertension when its effect subsides.	15
Dexmedetomidine	Centrally acting α_2 -adrenergic agonist that produces hypotensive and sedative effects.	<i>IV</i> : infusion initiated with a 1 μ g/kg loading dose, administered over 10 min, followed by a maintenance infusion of 0.2-1.0 μ g/kg/hour. Great individual variability in hemodynamic and sedative effects; the dose must be carefully adjusted.	2 h.	Dry mouth, drowsiness, nausea, sedation, severe hypotension, bradycardia, and arrhythmia.	Use in the Intensive Care Unit. Can induce rebound hypertension.	16
Diazepam	GABA _A receptor agonist, exerts anxiolytic, anticonvulsant, hypnotic, and muscle relaxant effects.	<i>Oral or GT</i> : 5-7.5 mg (or 0.1 mg/kg) every 4-6 hours. <i>Rectal</i> : 0.1 mg/kg every 3-4 hours.	20-100 h (36-200 h for main active metabolite desmethyldiazepam).	Respiratory depression, drowsiness, dizziness, fatigue, constipation, blurred vision, clumsiness.	Should not be used in patients younger than 1 year. Causes respiratory depression. Intravenous administration only in the Intensive Care Unit.	N/A
Metoclopramide	Central and peripheral dopaminergic receptor (D ₂) antagonist with antiemetic and prokinetic effects.	<i>Oral, GT or IV</i> : 5 mg every 8 h (0.1 mg/kg every 8 h in children < 10 years).	5-6 h.	Akathisia, dyskinesia, gait imbalance, incoordination, agranulocytosis, arrhythmia, neuroleptic malignant syndrome.	Crosses blood-brain barrier, potentially causing severe adverse effects.	N/A

Drug	Mechanism of action	Dosage	Half-life	Most common adverse effects	Comments	Ref.
Domperidone	Peripheral dopaminergic (D ₂ and D ₃) receptor antagonist with prokinetic effects.	<i>Oral or GT</i> : 10 mg every 6-8 h.	7 h.	Dysarthria, disorientation, headache, dizziness, dry mouth, arrhythmia.	Does not cross blood-brain barrier. Should not be used intravenously. Not available in the US.	N/A
Ondansetron	Serotonin 5-HT ₃ receptor antagonist with antiemetic effects.	<i>Oral, GT or IV</i> : 8 mg every 6-8 h.	4-6 h.	Headache, diarrhea, constipation.	Seldom effective in FD.	N/A
Tachycardia						
Propranolol	Non-selective β -adrenergic blocker; decreases heart rate and blood pressure	<i>Oral or GT</i> : 20 mg three times a day (60 mg/day); can be increased up to 120 mg/day.	3-6 h.	Hypotension, bradycardia, bronchospasm, headache, drowsiness, dizziness.	Also has mild anxiolytic effect.	N/A
Labetalol	α_1 - and β -adrenergic selective antagonist that decreases heart rate and blood pressure.	<i>IV</i> : 20 mg bolus over two minutes. Additional doses of 40 mg, then 80 mg may be administered every 10 minutes as needed. Additional 80 mg doses can be given to a total maximum dose of 300 mg/day. Additionally, labetalol can be administered by IV infusion at a rate of 2 mg/minute, with a maximum dose of 300 mg.	6-8 h.	Severe hypotension, bradycardia, bronchospasm, headache, drowsiness, dizziness.	Use in the Emergency Room or Intensive Care Unit to acutely decrease heart rate or blood pressure.	N/A
Orthostatic hypotension						
Midodrine	α_1 -receptor agonist that increases vascular tone and, therefore, blood pressure.	<i>Oral or GT</i> : 2.5-20 mg on an as needed basis, 30 minutes before getting up in the morning or before exercise. Maximum dose 40 mg/day.	3-4 h.	Supine hypertension, goose bumps, increased urination.	Low doses may cause significant increases in blood pressure due to denervation sensitivity.	27
Fludrocortisone	Synthetic mineralocorticoid, acts on the distal tubules of the kidney to enhance the reabsorption of sodium from the tubular fluid into the plasma. Increases blood pressure and the urinary excretion of potassium and hydrogen.	<i>Oral or GT</i> : 0.05-0.2 mg/day.	3.5 h.	Edema, muscle weakness, fatigue, supine hypertension, hypokalemia, arrhythmia, cardiac and renal fibrosis, renal failure, weight gain, depression, headache.	Potentially severe adverse effects; should be used in selected cases only. May be used in the treatment of hyperkalemia.	28

Drug	Mechanism of action	Dosage	Half-life	Most common adverse effects	Comments	Ref.
Anemia						
Erythropoietin	Glycoprotein hormone that increases erythropoiesis. Increased hemoglobin levels increase blood pressure via increased viscosity due to higher red blood cells and binding of nitric oxide.	SC: 25-125 U/kg three times a week, depending on hematocrit.	5 h.	High blood pressure, fever, dizziness, nausea, pain at the site of the injection.	Used in anemia of chronic disease. Use with caution in patients with cancer as it may increase the risk of tumor progression. Uncommon side effects include polycythemia, stroke, and thrombo-embolism.	29
Sialorrhea						
Glycopyrrolate (Glycopyrronim bromide)	Reduces salivary and pharyngeal secretions by blocking muscarinic cholinergic receptors.	<i>Oral or GT:</i> 1 mg three times/day; it can be increased up to 8 mg/day.	0.6-1.2 h.	Decreased sweating, dry eyes, urinary retention, blurred vision, tachycardia, constipation.	Does not cross brain-blood barrier. Contraindicated in glaucoma and prostatic hypertrophy.	38
Botulinum toxin (Onabotulinum toxin A)	Blocks local release of acetylcholine, thus reducing salivation	<i>Intraparotid injections:</i> 3 U/kg total dose (up to 100 U total dose).	The toxin should not reach systemic circulation. Effect may last 1-6 months.	Transient weakness of adjacent muscles (i.e., dysphagia, difficulties in chewing), dry mouth.	Can be performed with EMG or ultrasound guidance. Injections can be repeated depending on the therapeutic effect.	39
Gastroesophageal reflux						
Ranitidine	H ₂ receptor antagonist that reduces gastric acid output.	<i>Oral or GT:</i> 150 mg once a day at bedtime; it can be increased up to 300 mg/day.	2-3 h.	Very rare (<1%), including headache, dizziness and arrhythmia.	Dosage in patients with creatinine clearance < 50 mL/min is 150 mg/day. Cimetidine inhibits the metabolism of Diazepam, increasing its effect.	42
Omeprazole	Proton pump inhibitor that reduces acid output.	<i>Oral or GT:</i> 20 mg/day; can be increased up to 60 mg/day.	0.5-3 h, although the effect of a single dose may persist for 3 days.	Very rare (<1%), including headache, dizziness, nausea, and diarrhea.	Landoprazole, pantoprazole, esomeprazole. Should not be used in pediatric patients < 1 year of age.	42
Influenza						
Oseltamivir	Neuraminidase inhibitor with antiviral activity	<i>Oral or GT: Treatment of influenza:</i> <15 kg: 30 mg twice daily for	1-3 h. The active metabolite has a half life of 6-10 h.	Nausea, vomiting, diarrhea, abdominal pain, headache, renal	Also approved for the prophylaxis of influenza for high-	57

Drug	Mechanism of action	Dosage	Half-life	Most common adverse effects	Comments	Ref.
	against influenza A and influenza B viruses; against influenza A and influenza B viruses	Oral: 15-23 kg: 45 mg twice daily for 5 days. 23.1-40 kg: 60 mg twice daily for 5 days. >40 kg: 75 mg twice daily for 5 days. <i>Prophylaxis of influenza:</i> < 15 kg: 30 mg once daily for 10 days. 15-23 kg: 45 mg once daily for 10 days. 23.1-40 kg: 60 mg once daily for 10 days. >40 kg: 75 mg once daily for 10 days.		failure, exacerbation of psychiatric illness.	risk family members of an infected individual. Prophylaxis not approved for patients < 1 year of age.	
<i>Splicing-modification therapy</i>						
Phosphatidylserine	Phospholipidic component of cell layers that increases IKAP (ELP-1) levels	<i>Oral or GT:</i> 800 mg/day.	24 h (?)	Not described.	Clinical trials are underway.	96-98
Kinetin (6-furfurylaminopurine)	Cytokinin (plant hormone) that increases IKAP (ELP-1) levels.	<i>Oral or GT:</i> 10-30 mg/kg/day.	2 h.	Nausea.	Clinical trials are underway.	95

GT, gastrostomy; SC, subcutaneously; IV, intravenous; N/A, not available.