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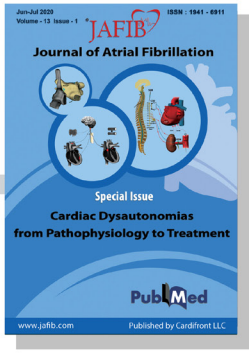

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Non-Pharmacological and Pharmacological Management of Cardiac Dysautonomia Syndromes

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Abstract

Vasovagal syncope, postural orthostatic tachycardia syndrome, and inappropriate sinus tachycardia comprise a heterogenous group of common autonomic disorders that are associated with significant symptoms that impair quality of life. Clinical management of these disorders should prioritize conservative non-pharmacological therapies and consider incorporating pharmacological agents for recurrences. The selection and titration of medications may be complicated by the occurrence of potentially overlapping pathophysiological variants, differences in specific clinical presentations, and commonly associated comorbidities. However, with appropriate long-term management and specialist input, most patients note both symptomatic improvement and functional restoration over time.

Introduction

Cardiac dysautonomias are a heterogeneous group of clinical disorders that are characterized by abnormal autonomic regulation of the cardiovascular system, often manifesting as forms of orthostatic intolerance. While these disorders generally are not associated with an increased risk of death, symptomatic orthostatic intolerance causes physical and psychological morbidities that significantly impair patient quality of life.[1–3] Unfortunately, there is a lack of broadly effective pharmacological treatment options, especially for those with complex comorbidities.

We will discuss management options for three common cardiac dysautonomias: (a) vasovagal syncope (VVS), (b) postural orthostatic tachycardia syndrome(POTS), and (c) inappropriate sinus tachycardia (IST). First, we outline the general non-pharmacological approaches to treatment, then describe medical therapies that may be effective in specific patient populations.

Key Words

Postural Orthostatic Tachycardia, Vasovagal Syncope, Inappropriate Sinus Tachycardia, Cardiac Dysautonomia, Management, Therapy.

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Definitions and Clinical Characteristics of Cardiac Dysauto nomias

Vasovagal Syncope

VVS is a common clinical problem that occurs at least once in over 35% of the general population.[4] It is defined as a syncope syndrome that usually (a) occurs with upright posture held for more than 30 seconds or with exposure to emotional or physiological stress; (b) features diaphoresis, warmth, nausea, and pallor; (c) is associated with hypotension and relative bradycardia; and (d) is followed by fatigue.[5] While VVS is generally benign, it can have a high recurrence rate that may warrant treatment due to associated physical traumas and psychological morbidities.[2]

Postural Orthostatic Tachycardia Syndrome

POTS is a multifactorial syndrome characterized by excessive orthostatic sinus tachycardia (≥30 bpm from baseline in adults) from supine to standing that occurs in the absence of orthostatic hypotension (fall in blood pressure of ≥20/10 mmHg).[5,6] Several potentially overlapping POTS subtypes may occur based on their pathophysiology, which may partially account for the variable efficacy of specific drugs in this population. The management of POTS may also be complicated by common comorbidities that might alter patient response to treatment and long-term prognosis.

Inappropriate Sinus Tachycardia

It can be challenging to differentiate IST from POTS due to overlapping clinical features, particularly excessive sinus tachycardia. IST is defined by a sinus node rate ≥100 bpm at rest while supine (or a mean 24-hour heart rate >90 bpm) that may be worsened by either physiologic or emotional stresses.[5] This high resting heart rate differentiates IST from POTS, in which the cardinal symptoms and tachycardia are exaggerated significantly by orthostatic stress. There may be overlap between the treatment approaches for POTS and IST, although there are few data supporting the efficacy of drug therapies for IST.

NON-PHARMACOLOGICAL MANAGEMENT

There is not a uniform approach to managing any of the cardiac dysautonomias. Treatment regimens should be set on a case-by-case basis using a graded approach that begins with non-pharmacological therapies. With proper adherence, these methods may eventually improve symptoms.

Patient education is a critical first step in managing autonomic disorders. Patients should be taught to avoid triggers and activities that might aggravate their symptoms, such as hot environments and prolonged standing. Patients and caregivers should also be reassured that most patients do well with appropriate and consistent management. However, it is important to be aware that there is no definite cure for these disorders and the goal of treatment is to minimize clinical burden over time.

All patients with chronic orthostatic intolerance should be encouraged to increase their water and salt intake to promote volume expansion. We recommend that, patients target three liters of water intake per day, accompanied by 8 to 12 grams of sodium chloride, in the absence of specific contraindications.[5–8] Salt tablet supplements may be necessary in patients who strongly dislike the taste of salt, but may be poorly tolerated in high doses. Many patients may experience nausea and vomiting with use of salt tablets. Gelatinized sodium capsules may be a better option in these cases to avoid gastrointestinal irritation.

Certain prescription medications may exacerbate cardiac dysautonomia symptoms. Many agents that reduce blood volume or decrease blood vessel tone can potentiate orthostatic intolerance. Where possible, common antihypertensives and heart failure medications (particularly diuretics and nitrates) should be reduced or withdrawn, although often this is not feasible.[5–8] Drugs that modulate sympathetic tone can have variable clinical effects depending on the condition in question. For example, norepinephrine transporter (NET) inhibitors have shown potential as a treatment for recurrent VVS,[9,10] but can worsen tachycardia and symptoms in POTS.[11]

Symptoms of orthostatic intolerance may be reduced by physical counter-pressure maneuvers aimed at increasing venous return.[5–8] These techniques have also been shown to reduce the likelihood of hypotension-induced fainting when performed during the prodrome of VVS.[12] Cardiac venous return can be further enhanced by the use of compression garments that provide 30-40 mmHg of counter-pressure and preferably reach the abdomen, as there is no evidence that compression garments excluding the lower abdomen offer any benefit.[13,14] Patient compliance is limited by poor tolerance.

Table 1: Summary of pharmacological agents suggested for the treatment of vasovagal syncope (VVS), postural orthostatic tachycardia syndrome (POTS), and inappropriate sinus tachycardia (IST). The strength of recommendations are marked using '+' or '+++' for weakly and strongly indicated therapies, respectively.

Drug	Disorder			Dosage Range	Clinical Considerations and Suggestions
	VVS	POTS	IST		
Atomoxetine	+			80 mg PO daily	Effective in controlled settings but not yet examined in a formal clinical trial with long-term follow-up
Clonidine		+		0.05-0.20 mg PO BID	May be associated with rebound tachycardia and hypertension
Desmopressin		+		0.1-0.2 mg PO TID	Only recommended for occasional use; monitor plasma sodium levels
Fludrocortisone	++	+		0.1-0.3 mg PO daily	Monitor plasma electrolyte levels, especially potassium
Fluoxetine	+			10-40 mg PO daily	May have variable clinical efficacy
IV Saline		+		1-3 L Over 1-3 hours	Only recommended as "rescue therapy", not for chronic use due to high risk of complications
Ivabradine		+	+++	5.0-7.5 mg PO BID	May be useful in patients with a predisposition to hypotension
Methyldopa		+	+	125-250 mg PO QHS or BID	May occasionally be associated with a rare Lupus-like syndrome
Metoprolol	+			50-100 mg PO BID	Consider only in those ≥42 years
Midodrine	++	+++		5-15 mg PO Q4H	Not recommended for use within 4-5 hours of sleep
Modafinil		+		100-200 mg PO BID	May improve cognitive symptoms; monitor for worsening tachycardia
Paroxetine	+			20 mg PO daily	May have variable clinical efficacy
Propranolol		+++		10-20 mg PO QID	Not well tolerated at higher doses
Pyridostigmine		+		30-60 mg PO TID	May increase gastrointestinal mobility

Abbreviations: IV, intravenous; PO, by mouth; QHS, prior to bedtime; Q4H, every 4 hours; QD, once daily; BID, twice daily; TID, three times daily; QID, four times daily

In patients with POTS, exercise training programs are a key component of management as they decrease upright tachycardia, improve symptoms and quality of life, as well as cause positive cardiac remodeling in patients who tolerate exercise long enough to complete the programme.[15] Importantly, exercise programs must be introduced gradually to avoid aggravating symptoms and slowly progress from non-upright activities (e.g. rowing machines, recumbent cycles) to upright aerobic exercises at least four times a week.[16] Patients should be informed that it can take 4 to 6 weeks of consistent adherence to these programs before benefits begin to take effect, and that these improvements may regress with the termination of regular physical activity.

In the context of VVS, POTS, and IST, pharmacologic agents should only be prescribed as adjuncts to existing non-pharmacological

therapies. That is, medications may be used if a trial of non-pharmacologic therapy is ineffective, or unlikely to provide sufficient symptom resolution. The remainder of this review will focus on pharmacological treatment options for each of these common cardiac dysautonomias. Table 1 provides a summary of these agents.

MANAGEMENT OF VASOVAGAL SYNCOPE

Individuals with a low burden of syncope typically do not require pharmacological treatment. Non-pharmacological approaches are generally sufficient to control infrequent VVS, but patients with recurrent syncopal episodes refractory to conservative therapies may benefit from pharmacological intervention. There have been several randomized controlled trials of various medical agents for the treatment of recurrent VVS in selected patient populations, yet there remains only modest evidence supporting the use of any one drug.[17]

Beta Blockers (Atenolol, Metoprolol)

The mechanism of beta blockers in VVS is thought to be through the blunting of elevated catecholamine levels that precede a syncopal event.[18] Few studies have examined the effect of beta blocker therapy on reducing community syncope events. One randomized trial evaluating the efficacy of atenolol found no difference in the recurrence of VVS episodes in symptomatic patients treated with drug relative to placebo.[19] Similarly, the first Prevention of Syncope Trial (POST), the largest single clinical study assessing beta blocker therapy in VVS, reported that metoprolol was no more effective than placebo in reducing the risk of recurrent syncope.[20] However, a pre-specified subgroup analysis from the POST trial showed an age-dependent effect of beta blockers in preventing VVS, with greater benefit among participants ≥42 years (hazard ratio [HR]: 0.53, 95% confidence interval [CI]: 0.25-1.10) compared to participants <42 years (HR: 1.62, 95% CI: 0.83-3.10).[21] As a result of these findings, beta blockers are not recommended for treatment of recurrent VVS in patients aged <42 years, but may be reasonable to use in those ≥42 years.[5,7] The use of metoprolol in VVS patients ≥40 years is currently being assessed in POST 5 (NCT02123056), an ongoing placebo-controlled clinical trial.[22]

In patients ≥42 years with a high clinical burden of VVS, metoprolol may be considered at 50 to 100 mg twice daily (Table 1). In the POST study, the most frequently noted side effect of metoprolol was increased fatigue, though some patients may also experience bradycardia, lightheadedness, or insomnia.[20]

Fludrocortisone

Fludrocortisone has mineralocorticoid activity that results in increased sodium and water retention, leading to expanded blood volume and enhanced venous return. It may be considered in those with suspected hypovolemia and an inadequate response to increased dietary salt and water intake. POST 2 was the first large, placebo-controlled clinical trial examining the efficacy of fludrocortisone for the prevention of VVS in patients with frequent episodes (defined as >1 syncopal spells and a Calgary Syncope Symptom Score >-3).[23] The study found a marginally non-significant 31% reduction in the risk of recurrent syncope among participants on fludrocortisone compared to placebo (p = 0.07). However, when the data was analyzed by time from the beginning treatment, a high event rate was found during the first two-week drug-loading period (i.e. a period of time where fludrocortisone would not be expected to have maximal drug efficacy). In a post hoc analysis, where syncope events occurring within the initial two-week dose-ranging period were censored, fludrocortisone significantly reduced time to first faint compared to placebo (HR: 0.51, 95% CI: 0.28-0.89, p = 0.019).

Given these findings, fludrocortisone may be considered in patients with frequent syncopal events at a stable dose of 0.2 mg daily (Table 1). Importantly, serum potassium levels should be monitored after dose adjustment and periodically during treatment due to the risk of drug-induced hypokalemia.

Alpha-1 Adrenergic Agonists (Etilefrine, Midodrine)

Etilefrine and midodrine are both alpha-1 adrenergic receptor agonists that enhance peripheral vascular tone and reduce venous pooling by both vasoconstriction and venoconstriction. Early placebo-controlled trials studied the efficacy of etilefrine in recurrent VVS, but failed to show a reduction in syncope burden with treatment.[24,25] Conversely, a meta-analysis of five studies (three adult and two pediatric populations) found a reduction in syncope recurrence and improved health-related quality of life in VVS patients with midodrine compared to placebo (risk ratio [RR]: 0.43, 95% CI: 0.27-0.68).[26] However, four of the five aggregated studies were either open-label or reported tilt-induced syncope outcomes. Only the Syncope Treatment and Assessment network NetherlanDs (STAND) trial was double-blinded and evaluated community syncope recurrence.[27] This study found no significant differences between the midodrine and placebo treatment groups, but only included 23 participants. POST 4 (NCT01456481) will be the first adequately powered clinical trial examining the efficacy of midodrine in syncope prevention.[22]

It is recommended that midodrine be dosed at 5 to 15 mg every four hours (i.e. 8:00 am, 12:00 pm, 4:00 pm) due to its short duration of action (Table 1). When properly dosed, midodrine is generally well-tolerated, but there is a risk of developing supine hypertension due to vasoactive drug effects. Accordingly, midodrine should not be taken within 4 to 5 hours of lying down. Other commonly reported side effects of midodrine include pilomotor erection ("goosebumps") and urinary retention.[26] Given the need for additional study on the efficacy of midodrine in VVS, the frequent daytime dosing (i.e. thrice daily), and the drug side effect profile, midodrine should be considered only for patients who are refractory to first-line drug therapies and who lack specific contraindications such as hypertension.[5,7,8]

Selective Serotonin Reuptake Inhibitors (Paroxetine, Fluoxetine)

There is considerable evidence supporting the role of central serotonin in the midbrain regulation of heart rate and blood pressure through the inhibition of sympathetic output.[28] Selective serotonin reuptake inhibitors (SSRIs) may modulate this mechanism by blocking the serotonin reuptake transporter (SERT), thereby enhancing nerve transmission and inducing the down-regulation of post-synaptic serotonin receptors, thus resulting in a blunted response to upsurges of central serotonin.[28] However, the benefit of SERT inhibition in the prevention of VVS is controversial and lacks supporting evidence. Limited clinical benefit was observed with

paroxetine or fluoxetine when compared to placebo or beta blockers.[7]

Despite the lack of data, select treatment guidelines recommend the use of SSRIs in patients with recurrent VVS,[7] but this class of medications are expected to exhibit highly variable clinical benefit. Paroxetine is fairly well-tolerated at 20 mg daily and fluoxetine at 10 to 40 mg daily (Table 1). However, side effects may include nausea, diarrhea, insomnia, and sexual dysfunction.

Novel Therapies

Norepinephrine Transporter Inhibitors (Reboxetine, Sibutramine, Atomoxetine)

Norepinephrine is released at central and peripheral sympathetic neuronal synapses and is primarily removed by active transport back into synaptic terminals by the NET protein. Some patients with VVS exhibit excessive norepinephrine reuptake, which results in inadequate vasoconstriction that may lead to syncope.[29] Inhibiting NET activity may preserve sympathetic tone in these patients during the vasovagal reflex and prevent syncope. The POST 6 study found that atomoxetine, a potent NET inhibitor used to treat attention deficit disorder, significantly reduced the likelihood of syncope on head-up tilt in patients with diagnosed VVS relative to placebo (RR: 0.49, 95% CI: 0.28, 0.86, p = 0.012).[9] Similarly, other studies with smaller sample sizes demonstrated that, reboxetine and sibutramine significantly reduced the likelihood of severe hypotension and bradycardia in healthy volunteers. NET inhibition elicited significantly elevated heart rates in the seconds preceding the vasovagal event in both VVS patients and healthy subjects, which in turn preserved mean arterial pressure.[10] Along with increasing heart rate, NET inhibition may have resulted in splanchnic venoconstriction, which acted to preserve stroke volume despite shorter filling times, thereby maintaining cardiac output.

Drugs that inhibit NET may also have affinities with SERT. Therefore, the selective potencies of drugs in this class should be considered. Reboxetine and atomoxetine are particularly selective NET inhibitors, while sibutramine is a potent NET inhibitor with marginally more SERT inhibition than the others. While all three of these drugs may be considered for the pharmacological treatment of recurrent VVS, only atomoxetine is clinically available in North America. Further research is needed with a placebo-controlled clinical trial to adequately assess the clinical relevance of NET inhibition for syncope management and its associated side effects with long-term use.

Based on preliminary tilt-based data from the POST 6 study, 40 mg atomoxetine taken twice daily may be useful in preventing VVS (Table 1), but it has yet to be determined whether a balance can be struck between this apparent benefit and drug side effects in clinical practice. Notably, patients may experience trouble sleeping when on the medication.

MANAGEMENT OF POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

POTS is a multifactorial syndrome that requires ongoing treatment. The goals of management are to reduce orthostatic tachycardia and associated symptoms, which typically include a combination of cardiac and non-cardiac manifestations. Cardiac symptoms include rapid palpitations, lightheadedness, chest discomfort, and dyspnea, while non-cardiac symptoms can include mental clouding, headache, nausea, tremulousness, blurred vision, sleep disturbances, and fatigue.

Heart Rate Restraint

Propranolol

Propranolol is a non-selective beta blocker that is useful for symptom reduction and heart rate attenuation at low doses, but it is poorly tolerated at higher doses despite greater orthostatic heart rate restraint.[30] It may be that some of the orthostatic tachycardia in POTS acts as compensation for other physiologic problems, such as low stroke volume, making severe heart rate attenuation counterproductive. Propranolol may complement exercise training programs as it slightly increases maximum exercise capacity.[31] Given the relatively short duration of action (4 to 5 hours per dose), propranolol can be taken as needed prior to physical activity at 10 to 20 mg per dose (Table 1).

Ivabradine

Ivabradine is a selective funny channel (I_f) blocker that reduces sinus node firing rate without other beta blocker properties. While ivabradine for POTS has not been studied in a controlled trial, a retrospective clinical case series demonstrated that the drug reduced patient-reported symptoms and tachycardia in over one-half of participants with continued use.[32]

Despite the limited evidence supporting the efficacy of ivabradine, it may be considered as an alternative to beta blocker therapy at 5.0 to 7.5 mg twice daily in symptomatic patients with a predisposition to hypotension or who experience severely exacerbated non-cardiac symptoms associated with hypotension (Table 1).[6] Importantly, ivabradine is contraindicated in pregnancy due to its potential teratogenic risk. As such, women with child-bearing potential should be provided with adequate contraception, otherwise alternate medications should be considered. Access to ivabradine may be limited due to lack of insurance coverage in North America since it is currently only approved for use in heart failure, and its use in POTS is off-label.

POTS Subtypes and Therapeutic Considerations

There are several postulated pathophysiologic causes of POTS. These mechanisms are not mutually exclusive but form a number of identifiable, potentially overlapping POTS subtypes that all share a final common pathway of excessive orthostatic tachycardia. The following agents have been grouped based on the pathophysiological variant that they may be most useful in addressing, but clinical usage is subject to physician discretion with ongoing follow-up.

Volume Expansion in Hypovolemic POTS

Up to 70% of patients with POTS experience hypovolemia, with a plasma volume deficit of approximately 13% on average.[33] This deficiency is magnified upon orthostasis due to a shift in blood volume to the lower extremities, resulting in comprised cardiac output and a subsequent increase in sympathetic nerve activity.

Fludrocortisone

Fludrocortisone is a synthetic aldosterone analogue that expands plasma volume by enhancing renal sodium and water retention. Although an attractive therapeutic option due to its physiologic effects, the evidence to support the use of fludrocortisone in POTS patients is limited to observational data.[34] Fludrocortisone should not be used at a dosage above 0.2 mg per day in a single or split dose (Table 1). Additionally, it is necessary to carefully monitor plasma potassium during fludrocortisone therapy, given the risk of drug-induced hypokalemia. This medication is otherwise generally well-tolerated, though side effects may include hypertension, fatigue, nausea, headaches, and edema.

Desmopressin

Desmopressin is a synthetic form of vasopressin that promotes blood volume expansion by increasing free-water permeability at the renal tubule and collecting duct, thereby enhancing free-water reabsorption without sodium retention. In one randomized cross-over study, oral desmopressin acutely lowered standing tachycardia and improved symptoms relative to placebo in a group of POTS patients.[35] However, long-term studies are needed to evaluate the safety profile of this approach prior to recommending desmopressin as a routine treatment for POTS. These concerns are largely due to the high risk of hyponatremia with daily use, especially given that all POTS patients are advised to increase their dietary water intake for blood volume expansion. At this time, it is recommended that desmopressin only be taken at a dose of no more than 0.2 mg once per day (Table 1). Plasma sodium levels should be regularly monitored in patients receiving this medication.

Intravenous Saline

Intravenous saline infusions should not be performed regularly in patients with POTS but may be used as a "rescue therapy" to rapidly augment blood volume in those presenting with severe symptoms and functional disability. This type of direct volume loading has been found to significantly reduce acute orthostatic tachycardia and associated symptoms when at least one liter of fluid is delivered over 1 to 3 hours (Table 1).[36,37] However, chronic saline infusions are only recommended for severely decompensated patients over short periods of time due to the high risk of access complications and infection with a central line.[5]

Peripheral Autonomic Modulation in Neuropathic POTS

Neuropathic POTS occurs in approximately half of patients and results from partial sympathetic denervation, particularly in the lower limbs, and inadequate vasoconstriction upon orthostasis.[38] The resultant decrease in venous return elicits a compensatory increase in sympathetic tone to maintain systemic blood pressure. Patients may benefit from autonomic modulation to enhance peripheral sympathetic tone.

Midodrine

Midodrine is commonly used in POTS patients to improve symptom control and reduce orthostatic tachycardia by enhancing vascular resistance and venous return, thereby decreasing the compensatory sympathetic outflow that occurs with hypotension and partial autonomic denervation.[6] Midodrine has a short half-life and requires dosing every four hours during the day, at 5 to 15 mg per dose, when given as maintenance therapy (Table 1). It should not be taken within 4 to 5 hours of bedtime. In some cases, it is suggested that midodrine may be used in a "pill in the pocket" approach for acute symptom management or as a supplement to other routine therapies.[6]

Pyridostigmine

Pyridostigmine is a peripheral acetylcholinesterase inhibitor that increases synaptic acetylcholine at autonomic ganglia and peripheral muscarinic receptors. It has been shown to significantly attenuate orthostatic tachycardia and improve symptoms when dosed at 30 to 60 mg three times a day in patients with POTS (Table 1).[39] Patients with diarrhea-predominant irritable bowel syndrome should avoid taking pyridostigmine as it increases gastrointestinal mobility and causes severe side effects in approximately 20% of patients, including abdominal cramps, nausea, and diarrhea.[40]

Central Sympatholytics in Hyperadrenergic POTS

Up to 50% of POTS patients may have elevated upright norepinephrine levels (≥600 pg/mL), with 20% of those showing features of the hyperadrenergic POTS subtype. Patients classified under this subtype of POTS tend to exhibit more prominent symptoms of sympathetic activation, in addition to an increase in blood pressure upon orthostasis and potentially more severe upright tachycardia.[41] Some of these individuals may benefit from the use of central sympatholytic agents, though they can be extremely sensitive to these medications. As such, central sympatholytics should initially be prescribed at the lowest therapeutic dose and gradually titrated upwards as tolerated to avoid worsen existing symptoms such as fatigue and mental clouding.[42]

Clonidine

Clonidine is an alpha-2 adrenergic receptor agonist that decreases sympathetic tone. Although there have been no controlled trials with clonidine, the drug has been found to reduce standing plasma norepinephrine levels, stabilize heart rate, and reduce orthostatic symptoms when taken consistently.[43] In POTS patients with hyperadrenergic features, clonidine has been shown to improve orthostatic tolerance in those refractory to beta blocker therapy when dosed at 0.05 to 0.2 mg at least twice per day (Table 1). Importantly, the short half-life of oral clonidine can cause rebound tachycardia or hypertension between doses due to a sudden return in sympathetic outflow. Clonidine patches have a longer acting delivery system and can at times avoid some of these adverse effects.

Methyldopa

Methyldopa has similar effects to clonidine but may be easier to titrate due to its longer duration of action. This medication is typically started at a single 125 mg dose at bedtime and may be increased to 125 mg twice daily for greater symptomatic control, if tolerated (Table 1).

Additional Therapeutic Considerations

Modafinil

Orthostatic cognitive impairments are fairly common in POTS patients and significantly impair quality of life. Modafinil is a

psychostimulant that may be used to improve mental clouding and concentration problems associated with POTS when prescribed twice a day at 100 to 200 mg per dose (Table 1).[42] While modafinil can improve alertness, it may also cause insomnia and worsen orthostatic tachycardia. Ongoing clinical monitoring is especially necessary when prescribing this medication.

Therapeutic Implications of Common Comorbid Conditions

There are several common comorbidities that are associated with POTS. These include Ehlers-Danlos syndrome (EDS), mast cell activation syndrome (MCAS), neuromuscular disorders, autoimmune neuropathy, and chronic fatigue.[6] The presence of these comorbid disorders can alter patient sensitivity to certain pharmacological agents or generate contraindications through the concurrent use of additional medications.

MANAGEMENT OF INAPPROPRIATE SINUS TACHYCARDIA

Clinical management of IST remains a substantial challenge, in large part due to a lack of understanding of its causes: autonomic dysfunction, intrinsic sinus node impairment, or both.[44] Controlling heart rate does not always lead to the improvement of symptoms or quality of life. Therefore, IST patients require close clinical follow-up and should be encouraged to emphasize non-pharmacological therapies. There is very limited data on pharmacologic therapeutic options in IST. Several pharmacological agents that are successfully used in POTS have been suggested for use in IST, including propranolol, fludrocortisone, and clonidine.[45] Unfortunately, beta-adrenergic blockade is not often effective and can cause adverse effects, which may be worse than the symptoms of IST itself. Other treatments have not been well tested in this patient population. However, there is emerging evidence that, ivabradine may be useful in the treatment of IST.

Ivabradine

One small randomized crossover study found that ivabradine eliminated over 70% of symptoms in IST patients, with nearly half experiencing complete symptom resolution.[46] In highly symptomatic patients refractory to monotherapy, ivabradine may be used in conjunction with metoprolol to enhance treatment efficacy and minimize the side effects that are typically associated with beta blocker therapy in this population.[47]

Conclusions

Cardiac dysautonomias are a multifaceted group of clinical disorders that significantly impact patient quality of life. Clinical management should take a graded approach and consider the clinical burden of disease, underlying pathophysiology, symptom presentation, and associated comorbidities. Patients require continued follow-up and possible medication adjustment due to the variable efficacy of commonly used drugs. However, the majority of patients experience marked symptom improvement and functional restoration with appropriate clinical management regimens that incorporate both non-pharmacological and pharmacological therapies.

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