IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Review Article
January 2020 Vol.:14, Issue:3

Pharmacological and Non-Pharmacological Interventions for Postural Orthostatic Tachycardia Syndrome (POTS): A Systematic Review of the Literature

IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

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Submission: 23 December 2019
Accepted: 29 December 2019
Published: 30 January 2020

HUMAN JOURNALS
www.ijsrm.humanjournals.com

Keywords: Postural orthostatic tachycardia syndrome, POTS, treatments, interventions

ABSTRACT

Background: Postural orthostatic tachycardia syndrome (POTS) is a form of dysautonomia disease that afflicts between 1,000,000 to 3,000,000 within the United States. POTS is characterized by an increase in heart rate and a drop in blood pressure upon standing; however, POTS patients can be symptomatic without drops in blood pressure. **Purpose:** The purpose of this review was to gather POTS treatment-associated research and analyze the best treatment modalities for patients. **Method:** A systematic review of the literature was conducted to gather articles. This study addresses the question: In patients with POTS, how effective is the use of pharmacological interventions on reducing symptomatic episodes compared with non-pharmacological interventions? **Findings:** The results indicated that a balance of pharmacological and non-pharmacological methods provides the best approach to symptom management in POTS, however; more research is necessary.

1. INTRODUCTION

POTS is a medical diagnosis that does not have a significant history of evidence-based research for viable treatment options. Proposed treatment options include pharmacological and non-pharmacological methods to ensure a better quality of life for POTS patients. Dysautonomia International propagated that common symptom treatments include increasing fluid volume, exercise, and taking various medications [1]. The purpose of this review was to gather POTS treatment-associated research and analyze the best treatment modalities for patients.

2. BACKGROUND

POTS is an autonomic nervous system disorder caused by cerebral hypoperfusion which causes many chronic debilitating implications for those afflicted [2]. These afflictions include cognition, depression, anxiety, and decreased quality of life. The trademark diagnostic criteria include an increased heart rate of 30 beats per minute or more during the ten minutes of a tilt table test. Associated criteria include signs of syncope, weakness, dizziness, fatigue, blurred vision, and lightheadedness. The patient typically does not have a history of orthostatic hypotension [3].

3. METHOD

The method of research was a systematic review of the literature on the topic of treatments for POTS. Databases used included the Cumulative Index of Nursing and Allied Health Literature (CINAHL), Medline and PubMed. The terms researchers used to find articles for review include *treatments*, *POTS*, *postural orthostatic tachycardia syndrome*, and *interventions*. Of the articles found using these keywords, only articles published between 2014 and 2019 were *included* in this study. The data presented in the articles were collected through a case study, observation, statistical analysis, qualitative review, controlled trials, research study, and meta-analysis. Articles belonging to the top six tiers of the evidence hierarchy were used for the study (see Figure 1).

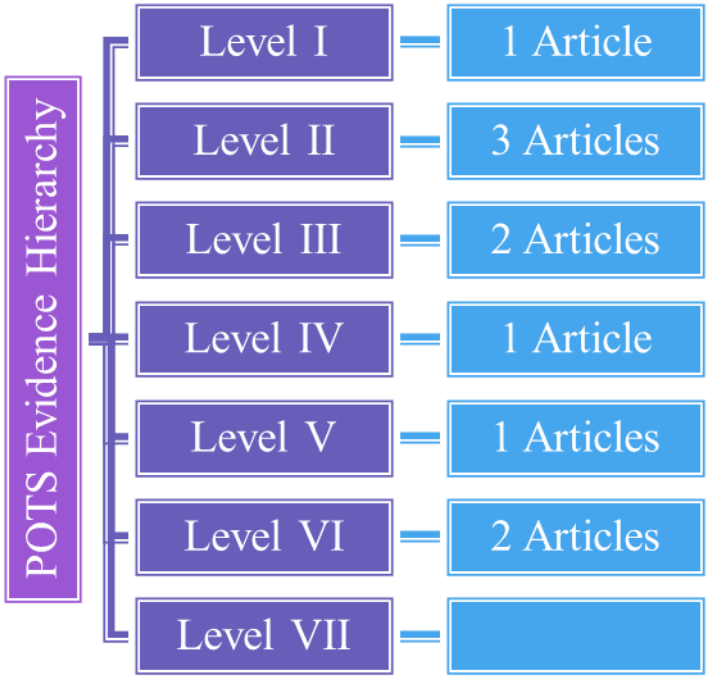

Figure No. 1*:* Levels of evidence used for articles in the study of POTS interventions.

POTS treatment options vary greatly with very little data supporting their use. The symptoms and comorbidities of POTS are treated in various ways. The effectiveness of the available treatment options is not well known. Several studies were reviewed to find the pharmacological and nonpharmacological interventions used and to evaluate the effectiveness of the treatments overall (see Table 1).

Table No. 1: ***Databases and Articles Used for Literature Review***

Database	Keywords	Articles Used	Articles Found
CINAHL	treatments, POTS, postural orthostatic tachycardia syndrome, interventions	4	274
Medline	treatments, POTS, postural orthostatic tachycardia syndrome, interventions	6	252

4. FINDINGS

This literature review included both pharmacological and non-pharmacological interventions in treating POTS. The efficacy rates of both methods of intervention were compared. The interventions were then categorized into either effective or ineffective treatment modalities for the management of POTS symptoms.

4.1 Effective Cardiovascular Medications

4.1.1 Beta-blocker therapy

Pharmacological interventions are commonplace among POTS treatment options. Wells et. al [3] describes a series of studies conducted on an accumulative of 200 patients who were treated with either non-cardiac selective beta-blockers or cardio-selective beta-blockers. Cardio selective beta-blockers had a pooled efficacy rate of 60% compared to 51% for non-selective beta-blockers. However, they acknowledge the need for randomized controlled trials to further analyze beta-blocking effects. The potential of beta-blockers is promising in helping to control heart-rate changes [3].

4.1.2. Vasopressor therapy

Vasopressor therapy has served as a pharmacological intervention to maintain adequate blood pressure in postural changes. Wells et al. [3] sampled more than 100 patients in various studies, which included adults and children. Sampled vasopressors included midodrine, octreotide, and droxidopa. Midodrine appeared to be superiorly efficacious compared to salt therapy in a study of pediatric patients. The efficacy of midodrine in pediatric studies was 66%. It was acknowledged that droxidopa had a low efficacy rate, but this was attributed to the fact that sampled patients have been previously unresponsive to vasopressor therapy. The efficacy of octreotide could not be adequately ascertained due to substandard efficacy recording [3].

4.1.3. Midodrine

In a study of midodrine efficacy in pediatric patients, 110 pediatric patients diagnosed with POTS were given midodrine while their supine and upright blood pressures measured for comparison [4]. Six children were not included in the study as they did not report for a follow-up. Children were given 2.5mg of midodrine per day without any other medications

for six months and then reported for a follow-up. Of the sampled children, 79 of them responded positively to therapy while 25 did not. Those who showed positive responses to therapy also displayed a noted decrease in their changing systolic blood pressure from a supine to an upright position [4].

4.2.Symptoms Specific Treatments

4.2.1. CNS stimulant therapy

There is a wide array of symptoms that can occur due to POTS. Boris and Bernadzikowski [5] conducted a retrospective review to determine effective medications in managing specific symptoms of fatigue and cognitive dysfunction. This class of medications is typically used to treat attention deficit disorder. Data from patient charts were collected and reviewed from the POTS program at the Children's Hospital of Philadelphia. A total of 722 patient charts were reviewed and ultimately 708 patients met inclusion. Specific medications addressed in this study included: methylphenidate, mixed amphetamine salts, dexmethylphenidate, lisdexamfetamine, atomoxetine, modafinil, and armodafinil. Methylphenidate had the highest individual rate of effectiveness at 53.1%, mixed amphetamine salts were the second highest at 47.1%, and the third-highest rate was modafinil at 43.6% [5].

Further investigation revealed that while some participants identified a relief in symptoms of fatigue and cognitive dysfunction, the medication was metabolized so quickly that the effect only lasted for three to four hours instead of the anticipated nine hours [5]. This required the second dosing of the medication, which was already in a long-acting formula. It was found that most participants required careful dosing of two different medications to receive the desired effect without unbearable side effects. Side effects from this class of medications included decreased appetite, stomach discomfort, and sleep disturbances such as insomnia, irritability or mood changes, headache, and tachycardia. These harsh side effects were the main motivation behind discontinuing the medication regimen. The researchers determined the therapeutic success of medications if five or more refills of medication were obtained by the participants. Based on this parameter, methylphenidate and mixed amphetamine salts were the two successful medications to treat fatigue and cognitive dysfunction [5].

4.2.2. Implantable loop recorders

Implantable loop recorders have also been used in studying patients suffering from POTS. Another study [6] found 450 patients who were admitted to the University of Toledo Medical Center due to syncope related to POTS. Thirty-nine of these patients had experienced at least four episodes of syncope within the last six months and these patients were the focus of this observational study. All 39 patients had a dual-chamber pacemaker implanted which could be automatically activated or patient activated. The reason for the insertion was to observe the mechanism of the patient's syncope and to increase understanding of the heart rhythm and symptom correlation. Before insertion, all patients had syncope regardless of the maximum tolerated dose of medical therapy. After the implantation of the loop recorder, all patients in the study were either free of syncope or had reduced occurrences; however, their symptoms of tachycardia and dizziness remained [6]. This observational study showed evidence that supports the use of implantable loop recorders for the treatment of syncope secondary to POTS. Since this treatment is focused on a subgroup of those suffering from POTS it may not be beneficial to those suffering from POTS without significant episodes of syncope. However, the population size should be increased, and subsequent studies should be performed to gather more evidence in support of this method.

4.3.Ineffective Treatments

4.3.1. SSRI therapy

A Vanderbilt University study focused on SSRI therapy as a potential pharmacological treatment modality for POTS patients [7]. Patient criteria included symptoms for at least six months, 37 out of the 39 patients were women. Patients were asked to describe several symptoms and rate their disruption. These symptoms included brain fog, tachycardia, and shortness of breath, trembles, transient angina, headache, dizziness, and nausea. Sertraline was the medication of choice at 50mg and alternating sitting and standing heart rate and blood pressure were measured every hour for four hours after drug administration. The results of the sertraline administration found no significant difference in standing heart rate elevations between the trial and control groups. Orthostatic tachycardia was still present in sertraline patients after four hours. Sitting blood pressure was discovered to be higher in the sertraline group. After two hours, standing means arterial pressure (MAP) and diastolic pressure was higher in sertraline groups. However, symptoms did improve in the placebo

group [7]. They acknowledged that sertraline did not exhibit any therapeutic effects, but also suggested that prolonged administration at a larger dose should be studied for efficacious effects.

4.3.2. Melatonin supplement

Another pharmacological method used in treating POTS is oral melatonin. Green et al. [8] tested the effects of melatonin in a randomized controlled trial. The subjects selected were patients of Vanderbilt Autonomic Dysfunction Center between 2004 and 2012. Considering the patients at this health center, certain criteria were required for eligibility including at least a six-month history of symptoms of POTS, absence of other chronic disorders causing orthostatic hypotension, 18-years-old and up, and the absence of extensive bed rest. With these criteria in place, there were 78 eligible participants from the Vanderbilt Autonomic Dysfunction Center.

Before administering the medication and beginning the study, the participants went through a diet and baseline study. Three days before the beginning of testing, the subjects were to consume a methylxanthine-free diet which included 150 mEq/day of sodium and 60 to 80 mEq/day of potassium [8]. The participants also had to discontinue their use of long-term medications at least five half-life periods before the study began. Certain medications such as selective serotonin reuptake inhibitors (SSRIs) were not discontinued and participants taking selective serotonin-norepinephrine reuptake inhibitors (SNRIs) were excluded from the study. The remaining participants went through a posture study to assess baseline heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and plasma catecholamines. After finding the baseline for each participant, the medication trials began. The patient's heart rate (HR) and blood pressure (BP) were taken immediately before three grams of melatonin or a placebo were given to the participants in a single-blind method. Participants were also asked to stand for 10 minutes, every hour for the first four hours after administration, while HR and BP were taken. The presence of symptoms commonly found in those suffering POTS such as mental clouding, blurred vision, shortness of breath, rapid heartbeat, tremulousness, chest discomfort, headache, lightheadedness, and nausea was assessed at hour two and four after the administration of melatonin [8].

Overall the patients did not have decreased symptoms after the administration of melatonin and their heart rate was lowered only moderately around the two-hour mark. They recognized

that the lack of symptom reduction could be due to the time of day that the melatonin was given. This study was only an acute administration of melatonin with a short follow-up, so it could be speculated that more effects may be seen with longer-term intervention as well as a longer period for follow-up [8].

4.3.3. Vagal nerve stimulation

A possible non-pharmacologic intervention for POTS is vagal nerve stimulation. Gadze et al. [2] performed a case study on a 29-year-old woman suffering from pharmacoresistant epilepsy who was also found to have POTS in a head-up tilt test. After performing an MRI, the patient was not eligible for neurosurgery due to malformations in the anatomy of her brain. Due to these malformations, they opted for a minimally invasive vagal nerve stimulator. After implanting the vagal nerve stimulator (VNS), the follow-up which consisted of a head-up tilt test (HUTT) occurred at one and three months. At each follow-up after implantation of the VNS the patient's results in the HUTT were normal, and after gradually increasing the VNS the patient had a significant reduction in seizure rate and disappearance of symptoms of POTS [2]. This case study showed significant results in the patient studied, however; a larger population size should be examined to further confirm its effectiveness. Additionally, this patient had a primary diagnosis of epilepsy which is not necessarily the case for all patients suffering from POTS. Patients with POTS as their primary diagnosis should be studied with the VNS to establish this treatments' effectiveness on POTS specifically.

4.4.Treatments with Large Time-Commitment

4.4.1. Intravenous normal saline therapy

The administration of intravenous (IV) saline infusions is one method of treating symptoms found in POTS. Ruzieh et al. [9] formulated an observational study to determine the effectiveness of IV saline infusion therapy programs in treating the symptoms of POTS. Participants were selected from 2010 to 2016 from the Syncope and Autonomic Disorders clinic. Inclusion criteria for participants included a medical diagnosis of POTS, failure of pharmacologic interventions, and a referral for IV therapy. The number of potential participants was 382, which narrowed down to 57 participants. IV saline was administered through either a peripheral line, a PICC line, or a port. The treatment regimen began with one liter of IV normal saline infused over 1-2 hours once a week. Depending on the participant's

response to initial treatment, the infusions were then titrated either up to two liters per week or down to one liter every two or four weeks. Out of the entire group of participants, only four participants reported that they did not experience an improvement in symptoms. Out of the participants who did experience relief from symptoms, 50 participants were able to wean from therapy in less than six months, and 44% in less than three months. Ruzieh et al. [9] recognized that the overall effectiveness of IV saline therapy presented may be impacted by the generally younger age and absence of any comorbidities. This study did not consider any other treatments that the participants could have been receiving at this time. While there is profound evidence supporting the administration of IV saline in therapy for POTS, other interventional methods need to be considered. It is also important to note that IV saline infusions occurred over a long period (three to six months), thus increasing the risk of infection at the insertion site of intravenous access.

4.4.2. Individualized exercise regimen

Exercise therapy is a non-pharmacological intervention in controlling symptoms of POTS. A case study outlined a potential exercise regimen to manage a POTS exacerbation [10]. A 34-year old female who experienced a POTS exacerbation after a stressful business trip was chosen for the case study. The participant presented with fever, severe fatigue, and malaise for twenty-five days that resulted in an inability to return to work during this time. After this time, the participant referred to a physical therapist for exercise intervention. The participant was tested for inclusion criteria in the form of a quiet standing test. At rest in a supine position, the participant's heart rate was recorded at 50 bpm, when the participant was standing the heart rate was recorded from 80-100 bpm. Based on these results, the participant met the inclusion criteria. The therapist began gathering baseline data by conducting two separate 1-Mile Track Walk Tests (1-MWT). On the first day, the participant recorded a time of 15:47 minutes and a heart rate of 133 bpm. On the second day, the participants recorded a time of 14:56 minutes and a heart rate of 150 bpm. A therapy regimen was constructed and included a physical therapy session one time a week for four weeks, endurance training four times per week, and strength training two times per week for four weeks. Based on parameters set in previous research studies, they developed a goal heart rate range during therapy of a minimum of 132-166 bpm with an ideal range of 152-166 bpm. Researchers conducted a final standing test, during which the patient had a heart rate of 67 bpm while supine and a heart rate of 90 bpm while standing for 10 minutes [10]. At the end of the four-

week training program, the participant reported relief from all symptoms and was able to successfully resume normal daily activities. While this case study provides evidence supporting the use of exercise programs in the management of POTS, further data should be gathered from larger population size.

5. DISCUSSION

The current review aims to address the question: In patients with POTS, how effective is the use of pharmacological interventions on reducing symptomatic episodes compared with non-pharmacological interventions? A combination of pharmacological and non-pharmacological interventions may support the best overall efficacy from symptoms for POTS patients. Neither form of intervention appears to objectively better serve patients over the other, but they both serve a purpose and may prove more effective when used in conjunction with one another. Beta-blockers, vasopressors, especially midodrine, and fluid volume resuscitation with normal saline appeared to be the most efficacious pharmacological interventions (see Figure 2).

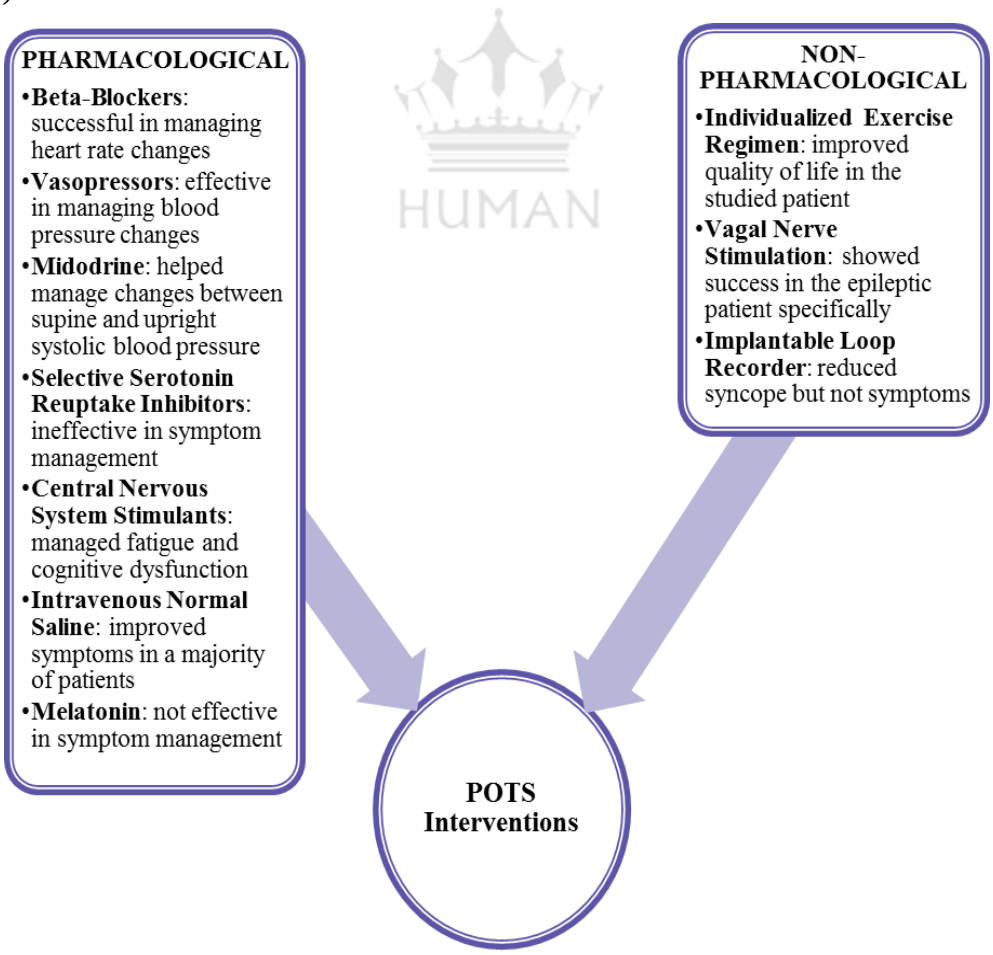

Figure No. 2: Pharmacological and Non-Pharmacological Interventions Efficacies

All levels of evidence were present in the research findings as a consequence of the limited research options available. The most authoritative research association was a systemic meta-analysis literature review provided by Mayo Clinic. Other research projects consisted of controlled research trials as well as case studies. Several themes were encountered throughout the research (see Figure 3). Cardio-selective beta-blockers and vasopressors, especially midodrine, were found to be the most effective in controlling tachycardia or blood pressure changes. A major issue regarding pharmacological therapies involves the ultimate side-effects that patients are bound to experience. This requires a delicate balance of dosing and testing multiple medications before desired effects may potentially be achieved.

Due to the wide array of symptoms that are present in POTS, certain treatments were capable of only targeting a select symptom. CNS stimulant medications were found to have an average of 53% effectiveness in treating symptoms of fatigue and cognitive dysfunction [5]. The drawback to this class of medication is the harsh side-effects, which may deter compliance. An implantable loop recorder effectively managed the symptom of syncope. These findings indicate the need for multiple approaches to treatment because of the wide array of symptoms that each patient can suffer.

While the case-study regarding exercise therapy is limited in only one participant, it shows promising results in the management of tachycardia and fatigue-associated symptoms. Another option in the management of POTS includes IV saline therapy. Ruzieh et al. [9] advocated for the effectiveness of IV saline therapies with only four participants of the study not experiencing relief of symptoms. The drawbacks to this kind of therapy include the need for constant intravenous access, which ultimately increases rates for infection in these patients. Comorbidities also need to be considered as some patients may not be able to handle added fluid into their bodies. While both treatments of saline infusions and an exercise regimen, effective in treating symptoms of POTS, they require a large time commitment and lifestyle changes. These factors may decrease compliance with therapy, thus reducing effectiveness. Interventions that were found to be ineffective were the use of melatonin and SSRIs. The use of vagal nerve stimulation was investigated to control symptoms of POTS secondary to epilepsy. The stimulation was found to be effective; however, this cannot be considered a general treatment to use because of its primary association with epilepsy [2]. Ultimately, this review provided evidence that the management of POTS may require a

combination of pharmacological and non-pharmacological therapies with a focus on individualized care plans.

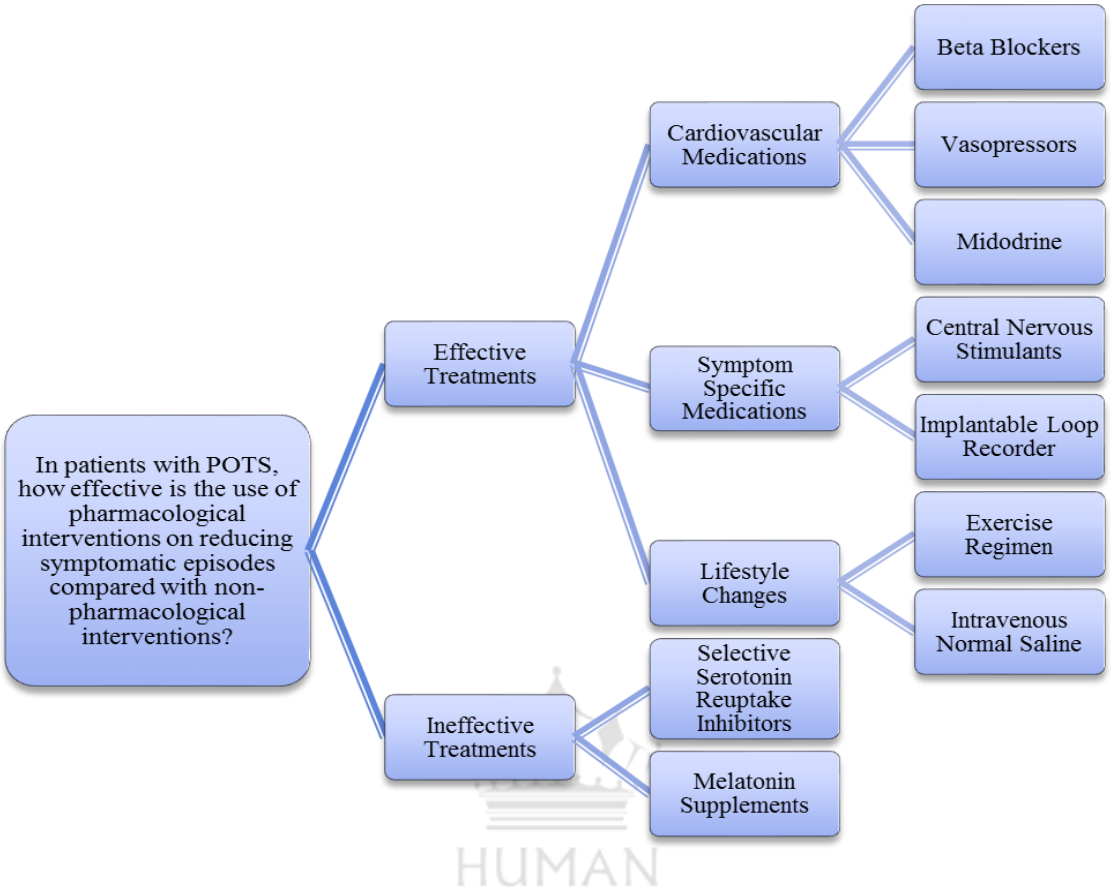

Figure No. 3: Themes for pharmacological and non-pharmacological interventions for POTS

6. CONCLUSION

POTS has a variety of explored treatment options. Research indicates that different individuals respond to different therapies. A combination of pharmacological and non-pharmacological treatment options may serve as the best treatment option for POTS patients. Volume loading and exercise training can improve physiological tolerance to physical activity while medications such as vasopressors or beta-blockers can increase the cardiac activity threshold ideally resulting in decreased syncope episodes. Treatment options should be evidence-based and improve the quality of life in patients with POTS. The relatively new diagnostic criteria for POTS limit the present treatment options. With further research, hopefully, more extensive and evidence-based treatment options may help to improve patient quality of life with symptom management.

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