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Efficacy of Pharmacologic Treatment for Orthostatic Hypotension in the Elderly Population

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by

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Abstract

The purpose of this literature review is to determine the efficacy and safety of pharmacologic treatments for orthostatic hypotension (OH), with an emphasis on researching the elderly population. In this review, three electronic search databases were utilized including PubMed, Google Scholar, and Dynamed from the years 1997 to 2019. Several keywords were used during the search. Criteria for chosen articles included that the article must be peer-reviewed, the studied population must have a median age of at least 50 years-old, at least 20 subjects must be involved, and the study must be published after the year 1995. The specific pharmacologic agents researched for the treatment of OH included midodrine, droxidopa, pyridostigmine, and fludrocortisone. There were 15 research articles chosen that included randomized control trials, systematic reviews, and meta-analyses. Although midodrine is the most researched and utilized pharmacologic treatment of OH, this drug may not be the best option when it comes to treatment in the elderly population due to an increase in supine hypertension. Pyridostigmine in combination with low-dose midodrine was found to be effective in relieving OH symptoms without increasing supine hypertension, but this evidence is based on limited randomized trials. More research is still needed to evaluate the efficacy and safety of these pharmacologic measures in the treatment of OH specifically in the elderly population and over a long period of time.

Keywords: Orthostatic hypotension, Aged, Drug therapy, Therapy, Mortality, Morbidity, Midodrine, Fludrocortisone, Pyridostigmine, Droxidopa.

Introduction

Orthostatic hypotension (OH) is prevalent in the elderly and is a significant cause of falls, hospitalizations, and deaths in this population. It is characterized by a decrease in blood pressure upon standing. In order to diagnose OH, there must be a decrease in systolic blood pressure (SBP) of at least 20 mm Hg or a decrease in diastolic blood pressure (DBP) of 10 mm Hg within 3 minutes of standing. In those over the age of 65, the prevalence of OH ranges from 16.2% in otherwise healthy individuals to over 50% in those that are hospitalized or in nursing homes (Biaggioni, 2014). There are a number of lifestyle changes and non-pharmacological measures that are used primarily in the treatment of OH, but sadly, it remains a large burden in the elderly population. The purpose of this study is to research the efficacy and safety of pharmacologic treatments available for OH in the elderly.

Methods

A literature review was performed using the electronic search databases PubMed, Google Scholar, and Dynamed. Both keyword and mesh terms were used to search the literature for pharmacologic and non-pharmacological treatment of OH in elderly adults. The search revealed a total of 101 studies after narrowing it down to human only studies and selecting articles focused specifically on therapy of OH. The literature was searched for pharmacologic treatment with midodrine, fludrocortisone, pyridostigmine, and droxidopa as these are the most commonly used drug treatments for OH. The search revealed limited original research studies for pharmacologic treatment in those over the age of 65, so the search was expanded to include studies that looked at all adults over age 18. Owing to this lack of age-specific evidence for

pharmacologic treatment, studies discussing the pathophysiology of OH in the elderly were compared with studies on drug treatment for all ages. Only 15 studies met the final criteria. This number was due to the fairly sparse data on the pharmacologic treatment of specifically OH and not other disease processes. In order to analyze specifically middle-aged or elderly patients, studies were only included in this literature review if their median age of patients was age 50 or greater. In addition to this, there were limited data that included an adequate sample size, and the 15 studies that were selected had to have at least 20 subjects, with most included studies having around 100 subjects. Studies were also excluded if they were not written in the past 25 years, with a study from 1997 being the earliest included.

Keywords: Orthostatic hypotension, Aged, Drug therapy, Therapy, Mortality, Morbidity, Midodrine, Fludrocortisone, Pyridostigmine, Droxidopa.

Statement of the Problem

The United States' population is continuously aging with around 14% of the population over the age of 65. This number is projected to increase to 17% over the next few decades (U.S. Census Bureau, 2018). Correspondingly, the contribution of OH to falls and mortality in the United States is likely to increase. Although OH is a common condition in the elderly population affecting nearly 20% of those over age 65, it is often overlooked and not treated effectively. The estimated cost due to falls on the health system is 23 billion dollars annually (Juraschek et al. 2016). Proper treatment of OH could decrease hospitalizations and overall mortality rates from preventable falls, thus decreasing costs in these areas. Primary care providers need to be informed on the safest and most effective treatment options for this condition, whether that is non-pharmacological interventions or drug treatments.

Research Question

Does adding pharmacological treatment to patients' non-pharmacological interventions prove beneficial in reducing the likelihood of falls and mortality in the middle-aged (>50) or elderly (>65) populations diagnosed with orthostatic hypotension?

Literature Review

A review of the literature shows that while there are original research studies on many pharmacologic treatment options for OH, there is a lack of age-specific evidence for the elderly population. To determine the safety and efficacy of these drugs specifically in the elderly population, physiologic mechanisms of OH in the elderly are compared to the original studies done on pharmacologic treatment for all age groups.

Non-pharmacological Treatments

Fan, Walsh, and Cunningham (2011) conducted a randomized controlled trial to evaluate the efficacy of sleeping-head-up (SHU) as a treatment for OH in older people. SHU is a common therapy that has been utilized in the treatment of OH in the elderly population for years.

Fan et al. (2011) studied 100 patients aged 60 and older with symptomatic OH. The patients were randomly divided into two groups; 66 were placed in the SHU group and 34 in the control group. The study was conducted over a six week period during which a 6-inch block was placed under the head of SHU group's beds. The patients were then assessed pre and post-intervention. During the measurement periods, a 24-hour ambulatory blood pressure was monitored. Along with that, SBP, DBP, and mean arterial pressures (MAP) were taken upon standing in the morning. Dizziness episodes were also reported before and after treatment.

The results from the study compared SBP after standing both before and after treatment. The SHU group showed an increase after standing of 1.98 mmHg SBP compared to before treatment while the control group showed an increase of 2.36 mmHg SBP (p=0.8). The results for DBP were similar with the SHU group showing an increase of 2.61 mmHg, and the control group showing an increase of 1.73 mmHg (p=0.28). These results showed that there were no improvements in blood pressure from baseline for either the SHU or control group. Regarding reports of weekly dizziness episodes, the SHU group reported an average of seven episodes of dizziness a week pre-treatment and .26 episodes post-treatment (p=0.0039). Comparatively, the control group reported an average of seven dizziness episodes a week pre-treatment and two episodes post-treatment (p=0.0013). However there was no statistically significant difference found with dizziness symptom relief between the SHU and control groups (p=0.038).

One limitation of this study was that part of the results were based on patient symptom reports. Another limitation was that it was hard to monitor sleeping position in this study, or if the patient slept consistently in a position that kept their head elevated on the 6-inch block.

The information from the study by Fan et al. (2011) demonstrates the effectiveness of one of the non-pharmacological treatments that is often used in the treatment of OH in the elderly population. It provides statistical data on the effectiveness of SHU as a treatment for OH, which can be compared to pharmacologic treatments later in the literature review. The data reveals that while SHU is a treatment that is often used in OH, it was not effective for improving blood pressures in those over the age of 60.

Okamato et al. (2016) conducted a randomized control study to compare the efficacy of splanchnic venous compression to midodrine in the treatment of OH. This study also provides

information as to whether venous compression and midodrine together produce a greater improvement in orthostatics than either treatment alone.

The study conducted by Okamato et al. (2016) was a single-blind, randomized, crossover control trial that was done over a period of four days. It included 21 autonomic failure patients aged 64 and older with a diagnosis of OH. On each day, patients received a different intervention in which the order was randomized. The treatments included either a dose of placebo, placebo plus the abdominal binder, midodrine alone, and midodrine plus the abdominal binder. Midodrine dosing ranged from 2.5 to 10 mg depending on the patients' dose at home. Systolic blood pressure was measured both seated before and standing one-hour post treatment. Patients were instructed to rate the severity of their orthostatic symptoms using the Orthostatic Hypotension Symptom Assessment (OSHA) Score.

The OSHA Score consisted of six items: dizziness, vision changes, trouble concentrating, weakness, fatigue, and head, neck or shoulder discomfort. Patients could rate each symptom on a scale of 1-10 before and after standing.

The results showed midodrine alone increased standing SBP by 16±3 mmHg ($p=0.010$) and splanchnic venous compression increased standing SBP by 12±4 mmHg ($p=0.019$) compared to pre-intervention SBP. These results were significant in comparison to placebo, which had an increase in standing SBP of 1.9 mmHg. Midodrine in combination with splanchnic venous compression produced a greater increase in standing SBP than either alone, with an increase of 23±4 mmHg, but the difference was not found to be statistically significant ($p=0.068$). Also of note is that midodrine increased seated SBP by 31±5 mmHg compared with placebo at an increase of 9±4 mmHg ($p<0.001$). In regard to OSHA Scores, the patients'

symptom burden decreased with both splanchnic venous compression and midodrine compared to placebo. With venous compression, OSHA score decreased from 21.9±3.6 to 16.3±3.1 post-treatment ($p=0.032$). With midodrine, OSHA score decreased from 25.6±3.4 to 14.2±3.3 post-treatment ($p<0.001$). Another interesting note was that symptom control was reported to be the greatest with midodrine and venous compression used simultaneously with an OSHA score of 12.9±2.9.

One limitation of this study was the small sample size of 21 participants. Another limitation was the symptom control results were based on self-reported data from the participants versus quantitative measures like the standing SBP. Lastly, blood pressures were only measured for 10 minutes once the patient was standing; more studies are needed to assess the long-term efficacy of these treatments.

The information in this randomized control study is beneficial to this research project because it directly compares a non-pharmacological treatment, venous splanchnic compression, to midodrine in the treatment of OH in the older population, with the mean age of participants being 68. It provides statistical data on blood pressure values before and after treatment and also reports on improvements in patient symptoms.

Robinson, Pearce, and Frith (2018) conducted a qualitative study to determine the acceptability of therapies for OH in the elderly population. This study was the second phase following a study of efficacy for non-pharmacological treatments of OH including bolus water drinking, compression stockings, abdominal compression, and physical counter-maneuvers.

The study conducted by Robinson et al. (2018) included 25 people aged 60 and older recruited from a Falls and Syncope Clinic. Each patient had undergone treatment for OH with

four different non-pharmacological measures; bolus water drinking, compression stockings, abdominal compression binders, and physical counter-maneuvers (tensing lower limbs and abdominal muscles). The methods for this study utilized extensive interviewing of each participant and their opinions on tolerability, perceived barriers, and potential solutions for each of the four OH interventions. Bolus water drinking was reported to be well tolerated, and 18 out of the 25 patients' consumed the full 480 ml of water. Patients expressed barriers to this intervention included it being too tedious to drink each time prior to standing and the quantity of water being too much to consume. Other concerns included how it may impact urinary frequency. Potential solutions reported by patients were to add fruit juice or tea to improve flavor or reminding themselves that the bolus of water will improve their symptoms. Compression stockings were reported quite tolerable and comfortable by the patients. The barriers to compression stockings included difficulty in application and intolerable itching. Potential solutions reported were having someone around to apply the stockings, however this intervention was not an option for many of the patients surveyed. Abdominal compression binders were tolerated by some of the patients and reported to be comfortable, while others found them unbearable because they made them sore. The barriers reported with abdominal binders were application and comfortability. Potential solutions reported were wearing the binder for shorter periods of time. Lastly, physical counter-maneuvers were the most popular among participants due to convenience. Some barriers with physical counter-maneuvers were efficacy and concerns about symptoms not being improved. Potential solutions were more thorough training in how to perform the maneuvers in order for them to work the most effectively. Overall, the results of this

study show that non-drug therapies are not widely accepted or consistently used in the treatment of OH.

The limitations of this study include data collection through means of oral reports from agreeable participants. The results were based solely on self-reported data with regard to OH non-drug treatment options. Another limitation of this study was a small sample size of 25 participants.

This qualitative study is beneficial because it discusses the barriers to traditional non-drug treatments of OH. The data reveals that there are often adherence problems regarding non-drug treatment options, and not all treatment options are universally acceptable in the elderly population.

Efficacy of Midodrine

Low, Gilden, Freeman, Sheng, and McElligott (1997) conducted an original study to evaluate the effectiveness of midodrine in elevating SBP along with reducing symptoms of lightheadedness in patients with OH.

The methods of the study by Low et al. (1997) included 171 patients in a double-blind, multicenter, randomized parallel-group study. The patients included were over the age of 18 years old and had a diagnosis of OH. The average age of a patient included in the study was 60 years old. The study lasted six weeks, with the first week and last two weeks being washout periods in which all patients received placebo. During weeks two through five of the study, patients were separated into randomized groups to receive either placebo or 10 mg of midodrine three times a day. There were 82 patients assigned to the midodrine group and 89 patients to the placebo group. Baseline values of supine and standing blood pressures were taken at the

beginning and end of the study during the washout period. Throughout the entire six week long study patients had blood pressures and orthostatic symptoms of dizziness analyzed and recorded weekly. Symptoms of dizziness were analyzed on a scale of how often they had been present in the past week. The scale was from 1-10, with one representing symptoms of dizziness "always" and ten having symptoms "never" upon standing.

The results of the study revealed that standing blood pressure in the midodrine treatment group had statistically significant improvement when compared to the placebo group ($p<.001$). The midodrine group had increased standing SBP by an average of 21.8 mmhg throughout the treatment compared to the placebo group with an average increase in standing SBP of 4.7 mmhg. The results also showed a statistically significant improvement of symptomatic lightheadedness after the second week of treatment in the midodrine group compared to placebo ($p=.02$). On the scale created for lightheadedness, the average answer for the midodrine treatment group was 5.3 versus 4.4 in the placebo group, indicating fewer lightheadedness events. It is also of note that both the placebo and midodrine treatment groups had less lightheadedness than baseline values, which had an average of 3.4 on the lightheadedness scale. The results also reported some adverse events with the use of midodrine. The most common adverse events reported were piloerection ($n=11$), pruritus ($n=8$), paresthesias ($n=7$), and urinary retention ($n=5$).

One limitation to this study for this project was that it looked at patients aged 18 and older, where this project has the main focus of researching the treatment of orthostatic hypotension in the elderly. This being said, the average age of a patient in this study was 60 years old, which is close to the target age for this research paper. This study is beneficial to this project because although the ages studied vary, the mechanism studied behind the orthostatic

hypotension is the same; autonomic failure. The information in this article is helpful because it provides statistical data on the efficacy of midodrine in regard to the treatment of autonomic orthostatic hypotension. This data can be related to treatment options for OH in the elderly due to the similar mechanism of action behind OH in these populations studied.

Smith, Wan, Much, Robinson, and Martin (2016) also conducted a study in order to assess the effectiveness of midodrine in the treatment of symptomatic OH. Midodrine is a short-acting pressor agent that has been approved for the treatment of OH in the United States since 1996.

A double-blind, randomized, crossover, multicenter study was conducted on patients greater than 18 years of age. There were 20 participants in the study with a diagnosis of severe OH and a mean age of 61.4 years. To qualify for the study, patients had to have been taking midodrine for at least three months prior to the study and had symptoms upon standing of either dizziness, feeling faint, or lightheadedness. The beginning of the study consisted of getting baseline blood pressure values over 28 days of the patients' regular midodrine dose. During day one of the study, midodrine treatment was removed. The patients were eligible to continue if their Orthostatic Hypotension Symptom Assessment (OSHA) score increased by 4 points and if they were positive upon doing orthostatic blood pressure testing. On day two of the study, patients were randomly assigned to groups and either treated with midodrine or placebo. One hour after treatment, tilt-table testing was performed. During this, patients were tilted from 0 to 90 degrees and held upright for 45 minutes. On day three of the study, patients were given the alternative treatment from the day prior and again underwent a tilt-table test with time to onset of syncopal symptoms recorded.

Results from the study done by Smith et. al (2016) revealed a statistically significant difference between midodrine treatment and placebo with the time to onset of syncopal symptoms in patients with symptomatic OH ($p=0.0131$). For midodrine treatment, the average time to the onset of symptoms was 1626 ± 186.8 seconds after initiation of the tilt-table test. In patients receiving placebo, the average time to the onset of symptoms was 1105.6 ± 186.8 seconds. There were six patients receiving midodrine who did not have any syncopal symptoms during the 45 minute tilt-table test compared to only one in the placebo group.

A limitation to the Smith et al. (2016) randomized control study was the small sample size of 19 individuals who met the final qualifications for the study. Another limitation regarding my research was that this study looked at all people aged 18 and older, instead of restricting it to only the elderly population, though the average age of a patient in the study was 61.4 years old.

This study is vital to this project because it discusses the efficacy of midodrine in the treatment of symptomatic OH. The middle-aged and elderly population often present with syncope and falls related to OH resistant to non-pharmacological treatments. This study is beneficial as the standards for the study were high with a solid methodology to establish evidence behind the efficacy of midodrine in reducing symptoms related to OH.

Efficacy of Fludrocortisone

Grijalva, Biaggioni, and Shibao (2017) conducted a study with the objective of assessing the relative safety of fludrocortisone compared to midodrine in the treatment of orthostatic hypotension. Grijalva et al. accomplished this by examining the incidence rates of hospitalizations from the years 1995 through 2009 for those patients on either fludrocortisone or

midodrine, but not both. This study also looks at the rates of congestive heart failure for patients on either of these medications.

Grijalva et al. (2017) gathered a cohort of patients with OH using TennCare data files, which is the state-based managed care Medicaid program in Tennessee. They studied patients in the cohort from 1995 through 2009. In order to qualify for the research, the patient had to be greater than 40 years of age, have a diagnosis of OH, and have a prescription of either midodrine or fludrocortisone. The median age of patients studied upon entrance was 67 years old. For each patient the research was initiated from the earliest date of prescription, and continued through death, study outcome, or the fill of a different OH medication. There were 1,324 patients studied initiating fludrocortisone, and 797 patients with midodrine. The main outcome that was monitored for these patients was all-cause hospitalizations, with congestive heart failure related hospitalizations studied secondarily.

The results revealed that fludrocortisone was associated with a greater rate of hospitalizations when compared with midodrine use (adjusted incidence rate ratio=1.2, 95% CI, 1.02-1.40). There were 617 hospitalizations in fludrocortisone users compared to 323 hospitalizations in midodrine users. It is also important to note that there was no statistically significant difference found in the incidence of CHF-related hospitalizations between midodrine and fludrocortisone. For fludrocortisone, there were 57 incidences of CHF-related hospitalization and for midodrine there were 33.

Limitations to this study included that while it was monitored and reported that the patients were filling their prescriptions, there was no way to monitor if the patient was actually taking either fludrocortisone or midodrine daily as prescribed. Another limitation is that the study

was not designed to analyze specific causes of hospitalization, but rather to observe and compare hospitalization rates in patients taking either fludrocortisone or midodrine to compare the safety of these medications.

The study done by Grijalva et al. (2017) is important to my research because it discusses the relative safety of midodrine and fludrocortisone in older populations. Considering these are two of the most prescribed pharmacologic treatments for OH, it is important to analyze the safety of these medications and possible adverse events that may occur from their use.

Rowe et al. (2001) conducted a randomized trial to study the efficacy of fludrocortisone in patients with a diagnosis of neurally mediated hypotension and chronic fatigue syndrome. To be included in the study a patient was required to have a 25 mmHg drop in SBP upon initiation of the tilt-table test from their baseline supine values. While the goal of the study was to determine if fludrocortisone could improve patient symptoms on a global wellness scale, they also analyzed if fludrocortisone would improve SBP during the tilt-table test.

This study was a randomized, double-blind, placebo-controlled trial. 100 patients greater than age 18 were studied with symptomatic orthostatic hypotension during a 2-stage tilt test prior to initiation of the trial. The patients were randomly assigned to receive either placebo or fludrocortisone acetate. There were 50 patients that received placebo, 50 that received fludrocortisone, and the study was nine weeks in duration. During the first week, patients receiving fludrocortisone were given 0.025 mg. This dose was increased to two 0.10 mg capsules a day for a week. Then for the remaining seven weeks of treatment, patients were increased to four 0.025 mg capsules per day. The patients were also monitored in the two weeks post-study. The placebo group was given capsules containing methylcellulose only. To measure the

outcomes of the study, patients were asked to complete a wellness score each day of the study. The global wellness scale has patients rate how they feel on a scale of 0 to 100, with 0 representing poor and 100 representing excellent. Patients also had a tilt-table test completed at the conclusion of the study during week nine of treatment. During this, their heart rate and blood pressure was monitored and compared to the pre-treatment results.

The results of the study done by Rowe et al. (2001) revealed that there was no significant improvement in wellness scores between the fludrocortisone treatment group and the placebo group ($p=.76$). Over the nine-week study, the fludrocortisone treatment group had an average wellness score increase of 7.3 points, compared to the placebo group with an average increase of 5.6 points. It is also of note that they considered more than a 15 point increase a substantial improvement in symptoms. There were only 12/50 subjects in the fludrocortisone group with a wellness score improvement of 15 points or more, and 8/50 people in the placebo group. The results from the study also revealed no significant improvement of systolic blood pressure after the table-tilt test when comparing the fludrocortisone treatment group to the placebo group ($p=.11$). SBP increased by an average of 10.0 mmHg in the fludrocortisone group, and 9.6 mmHg in the placebo group. Overall, fludrocortisone was not proved to be efficacious as monotherapy in the treatment of symptomatic OH during this study.

One of the limitations to this study include infrequent monitoring of standing blood pressures for patients. While symptoms were monitored daily during treatment using the global wellness scale, blood pressures were only taken during the beginning of the study to get a baseline, and then during the last week of treatment. Another limitation was that it studied all people greater than age 18, versus limiting research to the elderly population.

This study was beneficial to my project because it was a large study that looked at the efficacy of fludrocortisone in managing symptoms associated with hypotension. Along with midodrine, fludrocortisone is often used in the management of OH in the elderly.

Efficacy of Pyridostigmine

Byun et al. (2017) completed a study with the objective to compare the efficacy of pyridostigmine to midodrine in improving orthostatic blood pressure and associated symptoms. This study was done over a three month treatment period, as Byun et al. focused on obtaining long-term effectiveness of these pharmacologic treatments.

Byun et al. (2017) conducted a randomized, parallel study. There were 87 participants greater than 18 years of age with orthostatic intolerance. The average age of patients studied was 57.2 years. Orthostatic intolerance was defined as a drop in SBP by 20 mmHg or a drop in DBP by 10 mmHg within three minutes of standing. The patients were then randomized into three separate test groups to receive either 2.5 mg of midodrine twice a day, 30 mg of pyridostigmine twice a day, or a combination of 2.5 mg midodrine and 30 mg pyridostigmine twice a day. At baseline, orthostatic blood pressures were measured at 1, 3, 5, and 10 minutes after standing. Participants also answered the OH questionnaire (OHQ) to get a baseline value of their symptoms. The study lasted three months, with orthostatic blood pressure, heart rate, and OHQ measured again after one month and three months of time. The OHQ was rated on a scale of 0-10 with 0 meaning the absence of symptoms and 10 meaning maximal severity. The symptoms Byun et al. monitored from the OHQ included lightheadedness, dizziness, vision disturbance, weakness, fatigue, difficulty concentrating, and head/neck discomfort. The study also monitored for adverse events throughout the three-month trial.

The results revealed that orthostatic blood pressure improved in all treatment groups after one and three months of treatment. In the midodrine plus pyridostigmine treatment group, both standing SBP and DBP drops were reduced (p=.007, p=.001, respectively). For the midodrine only treatment group, there was only improvement in SBP and for the pyridostigmine group there was only improvement in orthostatic DBP. In addition to this, at one month, the percentage of patients that met the blood pressure criteria for OH was down to 47.4%, and at three months this was down to 43.1% of the patients treated. There was no statistical difference between treatment groups with the proportion of patients who met the OH blood pressure criteria at one or three months of treatment (p=0.841, p=0.459, respectively). In the midodrine plus pyridostigmine treatment group, the proportion of patients who met OH blood pressure criteria was the lowest compared to all other treatment groups at three months at 33.3%. Overall, the combination of midodrine and pyridostigmine had the most beneficial effect on controlling orthostatic blood pressure drops, but all three of the treatment groups were successful in improving orthostatic blood pressure. In regard to symptom control, midodrine alone had the greatest decrease in symptoms on the OHQ followed by midodrine and pyridostigmine, then pyridostigmine alone (p=0.037). Midodrine OHQ scores had decreased from 33.4 to 16.5 over the course of treatment, pyridostigmine and midodrine in combination OHQ scores decreased from 32.0 to 16.5, and pyridostigmine alone OHQ scores decreased from 37.2 to 22.6. So, while the combination of pyridostigmine and midodrine was the most beneficial in improving orthostatic blood pressure values, midodrine alone was better at relieving OH symptoms.

At the completion of the study done by Byun et al. (2017), 10 out of 87 patients reported adverse events. From these 10 patients, the proportion did not differ between treatment groups

(p=0.111). The most common adverse events reported were aggravated dizziness, headache, and gastrointestinal symptoms, all with mild to moderate severity. Due to these adverse effects, two patients discontinued treatment, but all of the other adverse events reported resolved spontaneously.

A limitation to this randomized trial was the inability to confirm that patients were taking their medications daily as they were prescribed since the follow up with the patients was restricted to one and three month time periods.

The study done by Byun et al. (2017) is vital to my research because it demonstrates the efficacy of both pyridostigmine and midodrine in the treatment of OH. While this study included patients from 18 to 87 years old, the mean age of the population studied was 57, which is close to the target population for this research paper. This study also examines the relative safety of these medications, which is essential when considering prescribing a new medication to someone in the elderly population.

Singer et al. (2006) conducted a study to determine the efficacy of pyridostigmine in improving OH. When this study was conducted, midodrine was the only drug shown to be beneficial in a placebo-controlled trial, but it often significantly worsened supine hypertension. Singer et al. studied pyridostigmine to determine if it had the potential to lower OH without worsening supine hypertension. Pyridostigmine's physiologic action in the body enhances ganglionic transmission, whereas midodrine activates alpha-adrenergic receptors, increasing vasoconstriction.

Singer et al. (2006) used a double-blind, randomized, 4-way cross-over methodology in this study. There were 58 patients studied inpatient at the Mayo Clinic Research Center in

Rochester, Minnesota. The patients studied by Singer et al. (2006) were 18 years or older with multiple system atrophy, pure autonomic failure, autoimmune autonomic neuropathy, diabetic autonomic neuropathy, or unspecified neurogenic OH. In order to fit the criteria for OH the patient had to have a SBP reduction of at least 30 mmHg, or a mean blood pressure reduction of at least 20 mmHg within three minutes of standing. The study lasted six days, and throughout this time period patients underwent four different treatments. On day one, baseline values for blood pressure were taken for each patient. Days two through five of the study were the treatment days. Patients were randomized to receive one of four treatments on each successive day. The four treatment modalities studied by Singer et al. were (1) 60 mg of pyridostigmine bromide, (2) 60 mg of pyridostigmine bromide and 2.5 mg of midodrine hydrochloride, (3) 60 mg of pyridostigmine bromide and 5 mg of midodrine hydrochloride, and (4) placebo. Day six of the study was a washout day. During each day of the trial, supine and standing blood pressures were monitored at 1, 2, 3, 4, 5, and 6 hours post-treatment. Along with blood pressure monitoring, at each hour patients were asked to rate their symptoms on a scale of 1-5 (no improvement-excellent improvement).

The results of the study done by Singer et al. (2006) revealed that there was a significant difference in the improvement of OH between pyridostigmine and 5 mg of midodrine hydrochloride and two of the other treatment groups (placebo, $p=0.002$; pyridostigmine and 2.5 mg of midodrine hydrochloride, $p=0.03$), and a nearly significant difference when compared to the third treatment group (pyridostigmine, $p=0.051$). The reduction in blood pressure drop upon standing was 34 mmHg for placebo compared to 27.2 mmHg for pyridostigmine and 5 mg midodrine hydrochloride. Singer et al. also found there to be a statistically significant difference

in the reduction of a blood pressure drop between pyridostigmine alone and placebo (27.6 mmHg and 34 mmHg respectively, $p=0.04$). The blood pressure increase upon standing happened across all treatment groups by one hour post-treatment. Using a linear regression equation, Singer et al. also discovered that there was a significant association between improvement in blood pressure at one hour post-treatment with an improvement of symptoms of orthostatic intolerance ($p<0.001$). Lastly, it is important to note that there were not any significant differences seen in supine blood pressure after treatment with pyridostigmine (systolic $p=0.36$, diastolic $p=0.85$).

A limitation to this study was the wide range in ages for the study population. There is a gap in the literature in regard to studies of specifically only the elderly population with pharmacologic treatment of OH.

The study done by Singer et al. (2006) is beneficial to this project because it highlights that pyridostigmine, either alone or in combination with 5 mg midodrine hydrochloride, can improve OH without aggravating supine hypertension. This is especially important in the elderly population that is being focused on in this project, because hypertension is extremely prevalent in this population. Worsening supine hypertension is a common problem that arises in the treatment of OH in the elderly.

Efficacy of Droxidopa

The purpose of the study done by Elgebaly, Abdelazeim, Mattar, Gadelkarin, Salah, and Negida (2016) was to search the literature to determine the safety and efficacy of droxidopa for the use of OH.

Methods used for this study included a literature search using the search engines PubMed, Scopus, Web of Science, and Cochrane Central. Keywords used in the search included

droxidopa, L-DOPS, orthostatic hypotension, multiple system atrophy with orthostatic hypotension, and idiopathic orthostatic hypotension. The results revealed four randomized control trials eligible to include in the meta-analysis. From these four studies, a total of 485 patients were analyzed. 246 patients were in the droxidopa treatment group, and 239 patients were in the placebo group. Dosing for the patients was determined in an optimization period prior to each randomized control trial. Each trial looked at the improvement of supine SBP and the improvement in OH symptoms.

Overall, the results revealed that standing SBP was improved more in the droxidopa group compared to the placebo group with a mean difference (MD) of 4.09 mmhg between the groups (CI 95% 0.36-7.82, p=0.03). The meta-analysis also showed that the OHQ symptom composite score was decreased by a greater amount in the droxidopa group compared to placebo with a MD of -0.61 (CI 95% -1.03 to -0.19, p=0.004). It is also of note that standing SBP and OHQ score improvement was only found to be statistically significant during the first week of treatment with droxidopa, when analyzing the four different studies. When compared to a treatment of 8 weeks in duration, the efficacy of droxidopa decreased. The standing SBP MD from week one to week eight decreased from 7.43 to 2.96.

Limitations to the study done by Elgebaly et al. (2016) include insufficient data regarding droxidopa's benefits for control of OH symptoms. More research is needed in this area in the future.

This meta-analysis is beneficial to this project because it analyzes several randomized control trials that study the efficacy of droxidopa in improving standing orthostatic blood pressure. While droxidopa has been shown to control OH symptoms in the short-term, more

research is needed in this area to determine the efficacy and safety of droxidopa long-term. Long-term knowledge of safety is especially important for patients in the elderly population who are more prone to adverse effects.

Kaufmann et al. (2014) conducted a study with the goal to discover if droxidopa is effective in improving symptomatic neurogenic OH. They measured outcomes with a symptom scale and improvements in standing blood pressure, and also looked into whether a reduction in symptoms correlated with an improvement in OH.

The study done by Kaufmann et al. (2014) was a randomized, placebo-controlled, parallel-group trial that included 162 adults aged 18 years or older with a diagnosis of OH. The average age of participants was 59.2 years. The trial was conducted between August 2008 and July 2010 at United States, Canadian, and European centers. The study began with each patient going through dose optimization. During this period, droxidopa was initiated at 100 mg three times daily. From there, it was titrated in 100 mg increments until each patient increased their standing SBP by 10 mmHg compared with their baseline value. Each patient was asked to give a self-rating of 0 on a scale of 0-10 for symptoms of dizziness or feeling faint. The maximum dose permitted was 600 mg. After the optimization period, each patient went through a seven-day washout phase with no pharmacologic treatment. Following the washout phase began the seven day double-blind treatment. The 162 patients were randomized to receive either droxidopa or placebo. In total, 80 patients were assigned placebo and 82 were assigned droxidopa. Throughout the study, Kaufmann et al. measured blood pressure and heart rate values at baseline, on each day of optimization, at randomization, and at completion of the study. These values were measured three hours post-dose during the treatment period. Kaufmann et al. also studied symptoms using

the OHQ. This questionnaire addressed lightheadedness, vision disturbance, weakness, fatigue, trouble concentrating, and head/neck discomfort. Along with these six symptoms, Kaufmann et al. also had patients rate the treatment impact on four daily activities: standing a short time, standing a long time, walking a short time, walking a long time. Each item was scored on a scale of 0 to 10.

The results found that there was a statistically significant improvement in standing SBP in droxidopa when compared to placebo (95% CI 1.1-13.5, p=<0.001). In droxidopa the mean increase in SBP was 11.2 mmHg, compared to placebo which had an increase in SBP of 3.9 mmHg. Also of note was a significant increase in supine SBP in droxidopa of 7.6 mmHg when compared to placebo treatment with an increase of 0.8 mmHg (95% CI 1.53-12.07, p<0.001). In regard to symptom control from randomization to the end of the study, patients had a decrease in OHQ score of 1.83 points for droxidopa compared to a decrease of 0.93 in the placebo group (95% CI 0.30-1.48, p=0.003). Along with this, Kaufmann et al. (2014) discovered that the droxidopa treatment group had an increase in standing SBP correlated with a decrease in OHQ scores for patients, meaning their symptoms were improving (p<0.001).

During the double-blind treatment portion of the study, 18% of droxidopa patients and 14% of placebo patients reported adverse events. The most common events reported were headache in 7.9% of droxidopa and none of placebo, dizziness in 3.7% droxidopa and 1.2% of placebo, and fatigue which was reported in 2.5% of both droxidopa and placebo.

Limitations in this study include the short duration of the study period; the double-blind portion of the study was one week in length, so the long-term efficacy and safety of droxidopa cannot be shown from this study. Another limitation was the absence of continuous blood

pressure monitoring. Blood pressure was only monitored at baseline and at the completion of the double-blind week of the study.

This randomized, placebo-controlled trial done by Kaufmann et al. (2014) is pertinent to this project because it gives statistical measures of the efficacy of droxidopa for the treatment of OH. It is also beneficial as it identifies some of the adverse events that can result from this treatment option.

Relation Between OH and Falls/Mortality in the Elderly Population

Biaggioni (2014) conducted a literature review to evaluate the efficacy of different treatments used in the management of OH. This review provides information on OH in the elderly, the pathophysiology behind OH, and both nonpharmacologic and pharmacologic management options for OH.

The methods used in this study included literature review of the treatment options available for the management of orthostatic hypotension. Keywords used in the search were orthostatic hypotension, hypertension, frail elderly, autonomic nervous system, and droxidopa. Research articles were used from the years 1986 through 2014. A total of 57 articles were chosen in the review. Biaggioni (2014) did not specify what specific search engines were used.

The results discussed how common OH is in the older community, especially in the frail elderly. Biaggioni (2014) found the prevalence of OH in the community older than 65 years is 16.2%, but it is greater than 50% in patients who are hospitalized or in nursing homes. Biaggioni found that autonomic impairment, or impairment of the baroreflex compensatory sympathetic activation, was the main mechanism behind OH being prevalent in the elderly population. Other common causes of OH are dehydration, volume depletion, and polypharmacy. Biaggioni found a

multitude of non-pharmacological and pharmacologic options for the treatment of OH. The first non-pharmacological measure is to remove any factors that may contribute to the patients' OH (ie., medications). Some common medications that may exacerbate OH are amitriptyline, diuretics, and alpha-blockers. Other non-pharmacological options include increasing salt and water consumption and using physical countermeasures when standing. Physical countermeasures include tensing leg and abdominal muscles upon standing, thereby improving venous return and cardiac output. Abdominal compression binders have also been found to be effective. Biaggioni also found a bolus ingestion of at least 16 oz of water to be effective. It can increase blood pressure within 5-10 minutes, with a peak impact at 30 minutes. This treatment measure is short-lived and needs to be implemented each time before a patient stands.

Fludrocortisone is a pharmacologic treatment available for OH that works by improving venous return by expanding intravascular volume. However the increase in plasma volume is transient and will return to baseline in two weeks. More research is needed for fludrocortisone's long-term efficacy. In his review, Biaggioni (2014) found that fludrocortisone should not be used in patients with congestive heart failure. Pyridostigmine is another medication available in the treatment of OH, and it works by facilitating neurotransmission in autonomic ganglia. It is not quite as potent as other agents used, but it has the benefit of only increasing blood pressure upon standing, without worsening supine hypertension. Midodrine was the first treatment approved by the Food and Drug Administration (FDA) for OH. It works to improve OH by increasing vascular tone and vasoconstriction, but can often significantly worsen supine hypertension. Another drug that is approved by the FDA for treatment of OH is droxidopa. Droxidopa improves OH by increasing the levels of norepinephrine in the periphery, thereby inducing

vasoconstriction of blood vessels. Droxidopa has been found to have very few adverse effects and be successful in improving OH. Overall, Biaggioni (2014) found that non-pharmacological measures can be efficacious when used consistently in mild OH. The two drugs FDA approved for the treatment of OH are midodrine and droxidopa, but these can sometimes worsen supine hypertension, which is a frequent comorbidity with OH especially in the elderly population. Other off-label treatment options for OH include pyridostigmine and fludrocortisone, but more studies are needed to assess the safety and efficacy of these pharmacologic management options.

The limitation in this literature review includes Biaggioni (2014) not disclosing the search engines used when finding his sources.

The study done by Biaggioni (2014) is beneficial to this project because it discusses specifically the physiologic mechanisms of OH in the elderly community and the possible treatments that can be used to address these issues. Many research studies on orthostatic hypotension treatments look at all ages in the adult population, and not just the elderly, so analyzing the physiologic mechanisms behind the disease is helpful to identify effective treatments.

Kearney and Moore (2009) conducted a literature review to evaluate the current options for management of orthostatic hypotension in older adults. This review provides information on the burden and consequences of OH in the elderly population, the physiologic mechanisms behind OH, the most studied treatments of OH, and the future research that is still needed in this area.

The methods utilized in this study include a thorough literature review using scholarly publications from the years 1951 through 2009. A total of 36 articles were selected for the review.

The results of the literature review included an examination of several topics surrounding orthostatic hypotension in the elderly. The review discussed that OH is a significant cause of dizziness, light-headedness, falls, fractures, and impaired mobility in the elderly population. Along with this, it stated the most common mechanism behind OH in this population is related to reduced alpha adrenergic responsiveness, leading to reduced cerebral perfusion. Other possible mechanisms include low renin levels, loss of arterial compliance, and disturbed cerebral auto-regulation. Regarding the treatment of OH, Kearney and Moore (2009) report that while non-pharmacological measures such as physical counter-maneuvers and compression stockings are most used and best researched, there is still some evidence that supports the use of pharmacologic anti-hypotensive agents. They also stress the importance of thorough examination of patients' medications and fluid intake prior to starting additional treatment. They conclude the best studied pharmacologic treatments for OH include midodrine and fludrocortisone, but these lack long-term information and large sample sizes. Other medications stated in this review that are used in the treatment of OH are droxidopa, octreotide, ephedrine, and yohimbine. Overall, more randomized trials are needed to evaluate the effectiveness of pharmacologic treatment in this condition.

The limitations of the review by Kearney and Moore (2009) include the use of articles which are outdated, but this is due to the lack of original research studies on this topic. There is also a lack of randomized trial data researching pharmacologic treatment options for this

condition in addition to small sample sizes within the studies that are available. Finally, there is a lack of age-specific evidence found in the literature regarding the treatment of OH.

This literature review is useful to this project because it provides current expert perspectives of different topics relating to the orthostatic hypotension issue seen today in the elderly community. It provides insight to the burdens, treatment options, and necessary research needed in the future regarding OH in the elderly population.

Mol et al. (2019) conducted a systematic review and meta-analysis in order to evaluate the association between OH and falls in the elderly population.

Methods used in this study included a systematic review combined with a meta-analysis. The search engines used were MEDLINE, PubMed, and EMBASE and studies were analyzed from the years 1946 to 2019. Search terms included orthostatic hypotension, postural hypotension, and falls. In order to be included in the review done by Mol et al. (2019), each study had to be 1) written in English, 2) conducted on a population of ages 65 and older, 3) blood pressure measurements done before and after postural change, 4) assessment of falls included in study, and 5) assessment of the falls association with OH. Studies were then included in the meta-analysis if a falls prevalence odds ratio (OR) was reported from the data on fall prevalence in patients with and without OH. Orthostatic hypotension was defined as a drop in SBP by 20 mmHg or DBP by 10 mmHg in the first three minutes after standing. In total, there were 63 studies included in the systematic review and 50 of these were included in the meta-analysis.

The results from the systematic review revealed that 24 of the 63 studies showed a positive correlation between OH and falls in the elderly population, with the other studies

reporting no association. The meta-analysis showed that from analyzing fall prevalence odds ratios, OH was significantly associated with falls (95% CI 1.50-1.99, $p<0.001$).

A limitation that was found in this systematic review and meta-analysis was that most of the studies were of moderate to low quality. While it was found that OH was positively associated with OH, there are no conclusions made about a causal relationship between falls and OH.

The study done by Mol et al. (2019) was beneficial to this project because it analyzed the literature to reveal that there is an association between OH and falls in the elderly population. Since OH is prevalent in the elderly population, it is essential to find the best possible management options of OH in order to reduce falls and hospitalizations.

Shaw et al. (2019) conducted a study with a goal of evaluating the relationships between OH, frailty, falling, and mortality in the elderly population.

The study was conducted by recruiting patients from two different long-term care facilities. A total of 116 older adults were assessed. In order to qualify for the study, the patient had to be greater than 65 years of age and Shaw et al. (2019) needed access to each patient's minimum data set (MDS). The MDS is a standardized assessment used across long-term care facilities throughout the United States. This assessment discusses 58 possible deficits, and scores each patient either a 0 (absence of condition) or 1 (presence of condition). From these deficits, Shaw et al. established a frailty index (FI-MDS). The average of the deficit scores was the FI-MDS, ranging from 0 (no deficits) to 1 (58 deficits). Some MDS deficit examples include: mood problems, social interaction, anxiety, feeling depressed, delirium, physical function, mobility and balance, cardiovascular disease, and bladder and bowel issues. Falling risk was also determined

for each patient from fall incidence reports. Additionally, 55 people from the studied population were also given a cardiovascular assessment. Patients SBP, DBP, heart rate, and mean arterial pressure were monitored, in the supine position for 15 minutes, and then upon sitting upright for 15 minutes. To conclude the study, Shaw et al. followed participants for three years after the date of the initial assessment. All-cause mortality was determined at this time with survival rates also determined.

The results from the study done by Shaw et al. (2019) revealed that there was a positive association between FI-MDS and age ($p=0.003$). There were 37 patients classified as non-frail ($FI < 0.27$) and 79 patients classified as frail ($FI \geq 0.27$). This study found that those who were frail had a significantly higher retrospective rate of falls than those who were considered non-frail ($p<0.0001$). It also showed that 64% of the patients studied had experienced a fall in the past year. The incidence of OH in the studied population was 62%. Shaw et al. found that the frailty predicted the presence of OH with 68% sensitivity and 60% specificity. Moreover, they found that frailty predicted prospective falls with 72% specificity and 36% specificity. Lastly, Shaw et al. discovered people who were frail had a higher mortality (20.5 ± 1.3 months) than those who were considered non-frail (27.1 ± 1.9 months, $p=0.006$). Overall, Shaw et al. found frailty to be associated with OH symptoms, falling risk, and all-cause mortality.

A limitation to this study included measuring orthostatic intolerance by having the patient move from supine position to sitting instead of standing. They used sitting upright measurements for OH because they did not think every patient would be capable of standing. Another limitation in this study was that fall risk was determined from looking at past fall reports versus looking at falls in the three years following the initial assessment.

This study conducted by Shaw et al. (2019) is beneficial to this project because it relates frailty, OH, falls, and mortality risk in the elderly population. It gives statistical significance to how these relate in the elderly population, and shows the need for more research in the treatment of these conditions for older individuals.

Discussion

Orthostatic hypotension is somewhat prevalent in people who are middle-aged and is even more widespread of a condition in the elderly population. The prevalence of OH in the community for those from the ages of 50-59 is around 4.2%. (Miller & Appel, 2014). For elderly individuals over the age of 65 in the community, that number is around 16.2% and in hospitalized or nursing home patients this increases to around 50% (Biaggioni, 2014). As people age, this condition is becoming increasingly important to screen for. Even though OH is prevalent in the community today, it is still often treated incorrectly or ineffectively, which leads to a greater percentage of falls and mortality rates, especially in the elderly population.

In order to effectively treat OH, there needs to be a patient-centered approach to care that focuses on not only improving SBP upon standing but also the patient symptoms associated with this as well. Before any other interventions, it is essential to rule out medications or inadequate fluid intake as a cause of OH. Once ruled out, the literature suggests the use of non-pharmacological measures as the initial treatment. Okamato et al. (2016) found abdominal binders to be the most effective non-pharmacological measure in the elderly population. A downfall to this method was that some patients reported the binders to be uncomfortable, so they were not compliant with use at all times. As highlighted by Robinson et al. (2018), bolus water drinking and physical counter-maneuvers were only moderately effective. Lastly, SHU and

compression stockings were found to be ineffective interventions for the treatment of OH in studies done by Robinson et al. (2018) and Fan et al. (2011). This information is essential for primary care providers understand, as these are often maneuvers that are attempted for the initial treatment of OH with minimal proof of benefit.

In regard to pharmacologic treatment options for OH, midodrine is by far the most well researched option and is FDA approved. Okamato et al. (2016) found midodrine to be effective at improving both standing SBP and symptoms such as lightheadedness in the elderly population. Studies done by Low et al. (1997) and Smith et al. (2016) also found this to be true, although these randomized studies included all adults over the age of 18. That being said, the average age in these studies was 60 and 64 years old, respectively, so the results are still applicable to the elderly population. The major adverse effect that occurs with midodrine is an increase in supine hypertension. So, while midodrine may be considered a first-line medication in the treatment of OH for the middle-aged population, or in those patients without underlying hypertension, it should be used with caution for those with hypertension. For this reason, it is a serious side effect to consider for treatment of the elderly population. The elderly are more susceptible to blood pressure fluctuations and are often using other medications to control their underlying hypertension in the first place.

Droxidopa is the second drug that was FDA approved for the treatment of OH in the United States. Elgebaly et al. (2016) and Kaufmann et al. (2014) both found droxidopa to be effective at increasing SBP upon standing in the short-term. In the study done by Elgebaly et al., it was of note that when measured at eight weeks of treatment compared to one week post-treatment, the effectiveness of droxidopa was no longer significant in improving OH. Droxidopa

works by increasing the levels of norepinephrine in the periphery, which increases constriction of blood vessels. Unfortunately, an adverse effect that was reported with the use of this drug was also a worsening of supine hypertension.

Fludrocortisone is another option that is used off-label for the treatment of OH. Fludrocortisone is a mineralocorticoid that works for OH by increasing plasma volume. Grijalva et al. (2017) compared the relative safety of fludrocortisone to midodrine and found that fludrocortisone users were more likely to be hospitalized. In addition to this, fludrocortisone should not be used in patients with congestive heart failure. Rowe et al. (2001) found that while fludrocortisone increased SBP in those with OH, it was not significant when compared to the placebo. Therefore, there is a need for more studies to be done on the effectiveness and safety of fludrocortisone in the treatment of OH, specifically for the elderly population.

Pyridostigmine is an acetylcholinesterase inhibitor that works by increasing norepinephrine release from post-ganglionic sympathetic nerves. Consequently, it improves OH only during orthostatic stress, meaning it works without worsening supine hypertension. Studies done by Singer et al. (2006) and Byun et al. (2017) found pyridostigmine to be effective at improving OH and symptoms associated with the condition. It was even more effective when paired with a low dose of midodrine, and in doing so it still did not affect supine blood pressure as much as midodrine alone. While there is definitely an opportunity for more research in regard to pharmacologic treatment of OH, I believe that pyridostigmine paired with a low dose of midodrine is the place to begin when using pharmacologic interventions to treat OH, specifically in the elderly population.

The main goal of this literature review was to establish the safety and effectiveness of different pharmacologic measures used to treat OH in the elderly population. There is a lack of age-specific evidence in regard to the pharmacologic treatment of OH in the elderly, and further studies need to be conducted in this population to determine the efficacy and safety of these drug treatments. It is important to note that many individuals in this population have underlying supine hypertension. Therefore, non-pharmacological measures should be maximized first while trying to treat OH. Pharmacological measures, such as pyridostigmine and low-dose midodrine, should be used on a trial basis after this to assess whether they relieve symptoms associated with OH.

Applicability to Clinical Practice

Orthostatic hypotension is seen regularly in primary care, and it is often difficult to treat effectively in the elderly population. Shaw et al. (2019) and Mol et al. (2019) conducted studies showing the correlation between the presence of OH and the likelihood of falls in the elderly population. Both studies showed that patients with OH were more likely to fall due to this condition than those without symptoms from OH. It is estimated that 23 million dollars annually is spent in the health care system due to falls (Juraschek et al., 2016). This literature review will benefit medical providers in how to treat orthostatic hypotension effectively in this population using evidence-based medicine. By doing so, patients will be healthier and safer. Furthermore, mortality rates and healthcare spending due to preventable falls may be decreased.

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