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Fludrocortisone for orthostatic hypotension (Review)

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[Intervention Review]

Fludrocortisone for orthostatic hypotension

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ABSTRACT

Background

Orthostatic hypotension is an excessive fall in blood pressure (BP) while standing and is the result of a decrease in cardiac output or defective or inadequate vasoconstrictor mechanisms. Fludrocortisone is a mineralocorticoid that increases blood volume and blood pressure. Fludrocortisone is considered the first- or second-line pharmacological therapy for orthostatic hypotension alongside mechanical and positional measures such as increasing fluid and salt intake and venous compression methods. However, there has been no Cochrane Review of the benefits and harms of this drug for this condition.

Objectives

To identify and evaluate the benefits and harms of fludrocortisone for orthostatic hypotension.

Search methods

We searched the following databases on 11 November 2019: Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase and CINAHL. We also searched trials registries.

Selection criteria

We included all studies evaluating the benefits and harms of fludrocortisone compared to placebo, another drug for orthostatic hypotension, or studies without comparators, including randomized controlled trials (RCTs), quasi-RCTs and observational studies. We included studies in people with orthostatic hypotension due to a chronic peripheral neuropathy, a central autonomic neuropathy, or autonomic failure from other causes, but not medication-induced orthostatic hypotension or orthostatic hypotension from acute volume depletion or blood loss.

Data collection and analysis

We used Cochrane methodological procedures for most of the review. We developed and used a tool to prioritize observational studies that offered the best available evidence where there are gaps in the evidence from RCTs. We assessed the certainty of evidence for fludrocortisone versus placebo using GRADE.

Main results

We included 13 studies of 513 participants, including three cross-over RCTs and 10 observational studies (three cohort studies, six case series and one case-control study). The included RCTs were small (total of 28 participants in RCTs), short term (two to three weeks), only examined fludrocortisone for orthostatic hypotension in people with two conditions (diabetes and Parkinson disease), and had variable risk of bias (two had unclear risk of bias and one had low risk of bias). Heterogeneity in participant populations, comparators and outcome assessment methods prevented meta-analyses of the RCTs.

We found very low-certainty evidence about the effects of fludrocortisone versus placebo on drop in BP in people with diabetes (-26 mmHg versus -39 mmHg systolic; -7 mmHg versus -11 mmHg diastolic; 1 cross-over study, 6 participants). For people with Parkinson disease, we found very-low certainty evidence about the effects of fludrocortisone on drop in BP compared to pyridostigmine (-14 mmHg versus -22.1 mmHg diastolic; P = 0.036; 1 cross-over study, 9 participants) and domperidone (no change after treatment in either group; 1 cross-over study, 13 participants).

For orthostatic symptoms, we found very low-certainty evidence for fludrocortisone versus placebo in people with diabetes (4 out of 5 analyzed participants had improvements in orthostatic symptoms, 1 cross-over study, 6 participants), for fludrocortisone versus pyridostigmine in people with Parkinson disease (orthostatic symptoms unchanged; 1 cross-over study, 9 participants) or fludrocortisone versus domperidone (improvement to 6 for both interventions on the Composite Autonomic Symptom Scale-Orthostatic Domain (COMPASS-OD); 1 cross-over study, 13 participants). Evidence on adverse events was also very low-certainty in both populations, but indicated side effects were minimal.

Observational studies filled some gaps in evidence by examining the effects in larger groups of participants, with more diverse conditions, over longer periods of time. One cohort study (341 people studied retrospectively) found fludrocortisone may not be harmful in the long term for familial dysautonomia. However, it is unclear if this translates to long-term improvements in BP drop or a meaningful improvement in orthostatic symptoms.

Authors' conclusions

The evidence is very uncertain about the effects of fludrocortisone on blood pressure, orthostatic symptoms or adverse events in people with orthostatic hypotension and diabetes or Parkinson disease. There is a lack of information on long-term treatment and treatment of orthostatic hypotension in other disease states. There is a need for standardized reporting of outcomes and for standardization of measurements of blood pressure in orthostatic hypotension.

PLAIN LANGUAGE SUMMARY

Fludrocortisone for the treatment of orthostatic hypotension

Review question

In people with orthostatic hypotension, does fludrocortisone prevent or reduce a symptomatic drop in blood pressure that occurs with changes in position (for example, from sitting to standing) and does it have unwanted effects?

Background

Orthostatic, or postural, hypotension is a condition in which blood pressure falls when moving from a seated or lying flat position to a standing position. Regular, reproducible symptomatic postural hypotension is an abnormal bodily response.

Orthostatic hypotension can be due to the heart failing to supply enough blood to the brain after a change in position. It can also stem from failures in blood vessel response to a change in position, for which there are many causes. Medications, dehydration, poor physical health and age all contribute to the problem. It is more common among people older than 65 and increases with age.

Symptoms include dizziness, lightheadedness and feeling faint. Some people have more general complaints such as weakness, fatigue, headache, visual blurring, trouble thinking, leg buckling, neck pain, breathlessness or chest pain. Some episodes of postural hypotension result in a faint, fall or 'black-out'. Symptoms decrease when blood pressure returns to normal, typically when the person sits, lies or, occasionally, falls down.

Fludrocortisone acetate is a man-made steroid that increases blood volume and improves the ability of blood vessels to respond to changes in position. Fludrocortisone is taken by mouth. It has also been associated with high blood pressure, swelling, congestive heart failure, low potassium (a blood salt), headache, sleeplessness and increased sweating. Other common medications for postural hypotension include midodrine and droxidopa.

Because postural hypotension results from many underlying diseases and conditions, it is important to understand the effect of fludrocortisone depending upon the underlying physical cause (heart pumping action or blood vessel reaction), by other underlying disease (Parkinson disease, diabetes, etc.) and by age. In this way, we can better understand whether different groups of people will be helped or harmed by using this medication.

We reviewed all the evidence about the effects of use of fludrocortisone in people with orthostatic hypotension.

Search date

The evidence is up to date to 11 November 2019.

Study characteristics

After in-depth screening of the scientific literature, we included 13 studies involving 513 participants. Only three studies used the most rigorous research design (randomized controlled trial [RCT]). Additionally, two non-RCTs filled gaps in the evidence. The randomized studies were small (a total of 28) and short-term (lasting three weeks or less). The randomized studies found that fludrocortisone reduced blood pressure drop compared to placebo (an inactive medication) in people with severe diabetic neuropathy, and compared to a medication called pyridostigmine when used in people with Parkinson disease. Among people with Parkinson disease, overall orthostatic symptoms were unchanged when fludrocortisone was compared to pyridostigmine but symptoms were reduced by both fludrocortisone and domperidone (an alternative medication) when compared. Side effects seen in these studies were minimal.

Study funding sources

Of the five studies that offered the best available evidence, two were at least partially funded by research foundations (such as the Dysautonomia Foundation), one had fludrocortisone tablets provided by the pharmaceutical company, and two did not report on funding.

Key results and certainty of the evidence

Based on considerable limitations in the available evidence, we cannot draw firm conclusions on the use of fludrocortisone for orthostatic hypotension in people with diabetes or Parkinson disease. The available evidence on blood pressure drop, orthostatic symptoms and adverse events in people with diabetes or Parkinson disease was very low-certainty. We still need more and better information about long-term use and about the effects of this medication among people with diseases besides Parkinson disease and diabetes.

SUMMARY OF FINDINGS

Summary of findings 1. Fludrocortisone compared to placebo for people with diabetes and orthostatic hypotension

Fludrocortisone compared to placebo for people with diabetes and orthostatic hypotension

Patient or population: people with diabetes and orthostatic hypotension
Setting: clinic for people with diabetes

Intervention: fludrocortisone
Comparison: placebo

Outcomes	Placebo	Fludrocortisone	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Blood pressure outcomes Follow-up: mean 3 weeks	Mean blood pressure drop was 39/11 mmHg	Mean blood pressure drop was 26/7 mmHg	6 (1 RCT)[a]	Very low	The evidence is very uncertain about the effect of fludrocortisone on blood pressure outcomes in people with diabetes and orthostatic hypotension.
Orthostatic symptoms assessed with: self-report Follow-up: 3 weeks	Not reported	4 out of 5 participants had improvements in orthostatic symptoms	6 (1 RCT)[a]	Very low	The evidence is very uncertain about the effect of fludrocortisone on orthostatic symptoms in people with diabetes and orthostatic hypotension.
Frequency and severity of postural lightheadedness	Not measured	Not measured	0	No studies	
Frequency of syncope	Not measured	Not measured	0	No studies	
Quality of life	Not measured	Not measured	0	No studies	
Serious or severe adverse events Follow-up: 3 weeks	Not reported	No serious or severe adverse events reported	6 (1 RCT)[a]	Very low	The evidence is very uncertain about serious or severe adverse events with fludrocortisone in people with diabetes and orthostatic hypotension.

RCT: randomized controlled trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]We downgraded the evidence three times: twice for imprecision (evidence based on 1 RCT of 6 people), and once for study limitations (process of randomization, allocation and masking not reported; 16% attrition in fludrocortisone group versus unclear attrition in placebo group).

BACKGROUND

Description of the condition

Orthostatic, or postural, hypotension is a condition in which a prolonged fall in blood pressure occurs upon standing after sitting or lying down. The consensus definition is a sustained reduction of systolic blood pressure (BP) of at least 20 mmHg or diastolic BP of 10 mmHg within three minutes of standing or head-up tilt to at least 60° on a tilt table (American Autonomic Society, American Academy of Neurology, Gibbons 2017). Orthostatic hypotension is detected by clinical examination, and may or may not cause symptoms (Freeman 2011). In people who have high blood pressure when lying down (supine hypertension), a reduction in systolic BP of 30 mmHg may be a more appropriate criterion for orthostatic hypotension because the size of the orthostatic BP fall is dependent on the baseline BP (Frith 2015).

The prevalence of orthostatic hypotension in people 65 years and older has been reported to be in the range of 5% to 30%, with higher prevalence linked to increasing age of the study population (Low 2008; Tilvis 1996). Orthostatic hypotension is more common in the institutionalized elderly (Freeman 2011). Orthostatic hypotension is frequently a comorbid factor for falls in the elderly (Gupta 2007). Recent evidence has suggested that traditional symptoms of orthostatic hypotension may be present in less than 50% of people with severe, chronic orthostatic hypotension (Arbogast 2009).

Orthostatic hypotension is the result of an excessive fall of cardiac output or defective or inadequate vasoconstrictor mechanisms, for which there are many causes and contributing mechanisms (Freeman 2011). Medications such as antihypertensive drugs and diuretics, antiparkinsonian medication (dopamine and dopamine agonists), antidepressants (particularly tricyclic agents), and sympatholytic agents and other vasodilators can cause or contribute to orthostatic hypotension (Gibbons 2017). Orthostatic hypotension can also occur because of inadequate fluid intake, particularly in elderly people. Other variables that affect orthostatic hypotension are gender, cardiac and vascular stiffness, prolonged lying, high ambient temperature and deconditioning (loss of strength and function that occurs when a person is very inactive) (Freeman 2011).

The autonomic nervous system contributes to the regulation of body states and processes, including blood pressure. Orthostatic hypotension can also therefore occur in people with neurodegenerative disorders affecting the autonomic nervous system. These conditions include multiple system atrophy (MSA), Parkinson disease and pure autonomic failure, and some neuropathies and ganglionopathies that affect autonomic nerves (Freeman 2007; Freeman 2011; Kaufmann 2003).

Characteristic symptoms of orthostatic hypotension include dizziness, lightheadedness, presyncope (faintness) and syncope (loss of consciousness) (Freeman 2008). Loss of consciousness is typically of gradual onset over seconds to minutes but can occur suddenly (Freeman 2011). Some people present with more general complaints such as weakness, fatigue, headache, visual blurring, cognitive slowing, leg buckling, neck pain, orthostatic dyspnea (breathlessness) or chest pain (Freeman 2008).

Symptoms of orthostatic hypotension subside as BP normalizes, typically when the person returns to a seated or a lying position (Wieling 1993).

Description of the intervention

Fludrocortisone acetate is a synthetic adrenocortical steroid with high mineralocorticoid activity that results in an increase in plasma volume and increased sensitivity of α-adrenoreceptors. Fludrocortisone is dosed by mouth at between 50 µg and 300 µg per day. Adverse events associated with fludrocortisone include hypertension, edema (swelling), congestive heart failure, hypokalemia (low potassium), headache, insomnia and increased sweating.

Other than fludrocortisone, common therapies for orthostatic hypotension include midodrine and droxidopa. Midodrine is an α-1 adrenergic agonist and is the most well established sympathomimetic agent used to treat orthostatic hypotension, approved by the US Food and Drug Administration (FDA) for this purpose (Low 1997). Its mechanism of action is direct stimulation of vascular α-adrenergic receptors with a resultant increase in flow resistance and BP (McTavish 1989). Droxidopa (L-threo-dihydroxyphenylserine) or L-DOPS, is a synthetic amino acid also FDA approved for treatment of orthostatic hypotension. Droxidopa is a precursor for norepinephrine requiring enzymatic conversion to the active amine by aromatic l-amino acid decarboxylase. It raises norepinephrine levels in postganglionic sympathetic neurons and enhances central nervous system norepinephrine production. The increase in circulating norepinephrine may also act as a hormone with BP-raising activity (Jordan 1998).

Less commonly-used therapies include direct or indirect adrenoreceptor agonists and other sympathomimetic agents phenylephrine, ephedrine, pseudoephedrine, phenylpropanolamine, methylphenidate and dextroamphetamine (Biaggioni 1987; Davies 1978b; Freeman 1999; Ghrist 1928; Jordan 1998). Treatments with any of the sympathomimetic agents can result in severe supine hypertension, so should not be used while lying down (Sandroni 2001). Pyridostigmine may act through potentiation of sympathetic cholinergic ganglionic transmission, leading to increased vascular tone, but only in the upright position (Singer 2003). The benefit of this therapy is a lower risk of supine hypertension than is seen with agents that result in direct vasoconstriction (Schondorf 2003).

Additional agents that may have efficacy in the treatment of orthostatic hypotension through other mechanisms include erythropoietin, non-steroidal anti-inflammatory agents, octreotide, and vasopressin (Armstrong 1991; Freeman 2003).

How the intervention might work

Fludrocortisone acetate alters BP through a variety of mechanisms including mineralocorticoid-induced sodium and water retention. Fludrocortisone binds to the aldosterone receptor, which increases activity of the distal tubule of the kidney, causing enhanced sodium ion and water transport into the plasma, and increasing urinary excretion of potassium and hydrogen ions (Campbell 1975b). Its effect on alleviating orthostatic hypotension is largely thought to be modulated through these actions. With chronic use, a BP-raising effect may persist, even though sodium retention and overall plasma volume normalizes through increased

peripheral vascular resistance (Armstrong 1991; Chobanian 1979b; Freeman 2003; Hoeldtke 1993). Other potential mechanisms may include sensitization of the vasculature to angiotensin II and norepinephrine (Hickler 1959; Van Lieshout 2000). Because orthostatic hypotension is a condition that results from multiple underlying diseases and conditions, it is important to analyze the effect of fludrocortisone by mechanism (peripheral versus central autonomic failure), by condition (Parkinson disease, diabetes, amyloid-induced orthostatic hypotension, pure autonomic failure, Lewy body disease, or MSA), and by age, as both the benefits and potential for harm may vary by subgroups. As an example, the BP-raising properties of fludrocortisone could potentially increase the risk of supine hypertension in certain subgroups, particularly the elderly.

Why it is important to do this review

There is inconsistent guidance on the use of fludrocortisone as first-line pharmacological treatment for orthostatic hypotension (Lanier 2011; Moya 2009; NICE 2013; Zesiewicz 2010). The evidence for the efficacy of fludrocortisone has not been evaluated in a Cochrane Systematic Review. This review evaluates the current evidence available on the efficacy of fludrocortisone for the treatment of orthostatic hypotension to better inform treatment recommendations and to highlight gaps in knowledge that require further investigation.

OBJECTIVES

To identify and evaluate the benefits and harms of fludrocortisone for orthostatic hypotension.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials (RCTs) and quasi-RCTs of fludrocortisone for orthostatic hypotension including cross-over and cluster-randomized trials. Quasi-RCTs are studies that closely mirror the design of a randomized trial, but use systematic rather than truly random methods of allocation (e.g. allocation by clinic date, date of birth, case record number, etc.). When data from RCTs and quasi-RCTs were lacking or at high risk of bias (that is, there are gaps in the evidence), we included certain types of non-randomized studies (NRSs). Current guidance for treating orthostatic hypotension is based on a small number of short-term RCTs (NICE 2013). Therefore, summarizing and evaluating NRSs could provide decision-makers with information on long-term benefits and harms, as well as dosing and other clinical approaches not adequately addressed in these trials. We utilized a hierarchical strategy to include NRSs in our analysis, to prioritize studies offering a higher certainty of evidence. To reduce the likelihood of NRSs' susceptibility to bias, we included prospective NRSs that compared distinct groups of participants who did and did not receive fludrocortisone (e.g. cohort or case-control). If these sorts of studies were not available, we included other types of uncontrolled NRSs with more than one participant (e.g. case series). All our selected PICOs (population, intervention, comparators and outcomes) applied to RCTs, quasi-RCTs and NRSs, with the exception of comparators, as we included uncontrolled NRSs if evidence from RCTs, quasi-RCTs and controlled NRSs were lacking or at high risk of bias. We did not apply any limitations by language or publication status.

Types of participants

We included all participants with orthostatic hypotension due to a chronic (non-acute, defined as present for at least eight weeks or more) peripheral neuropathy, a central autonomic neuropathy or autonomic failure from other causes (e.g. amyloid-induced or due to diabetes). We excluded from evaluation participants with medication-induced orthostatic hypotension and those with orthostatic hypotension from acute volume depletion or blood loss. We included both children and adults of any age.

We included studies that included only a subset of eligible participants if outcomes for eligible participants were reported separately, or at least 75% of the study population consisted of relevant participants.

Types of interventions

We included fludrocortisone compared to placebo, no treatment, another treatment or combination of treatments. If more than one treatment was included in the treatment arm, the same treatment (other than the fludrocortisone) had to be included in the comparator arm. In the event data from RCTs, quasi-RCTs and controlled NRSs were lacking or at high risk of bias, we accepted studies without a comparator. Our preferred minimum treatment duration was three weeks; however, we accepted all durations of treatment. We accepted all treatment dosages.

Types of outcome measures

We included all studies that met the above criteria. For all outcomes, we gave preference to studies that measured the outcome at least three weeks after initiating treatment; however, we accepted all time points. We also gave preference to studies that use validated scales for measurement of outcomes; however, we accepted all measurements. We also included studies that fit our inclusion criteria but did not include our prespecified outcome criteria, although these were not included in any formal analysis.

We defined the frequency of an event (i.e. postural lightheadedness; dizziness or presyncope; syncope; and falling) as the number of times an event occurs during a given time period, which converted to a standard measurement (number of events per week).

The pre-treatment to post-treatment period refers to the time immediately before treatment initiation (pre-treatment) to the last time a particular outcome measurement was collected for participants actively receiving treatment (post-treatment), even if participants continued to receive treatment after the final measurement was collected.

We pre-specified our definitions of minimum important differences. For systolic or diastolic BP, as no specific numerical value has been validated as the minimum important difference for change, we did not define a clinically important reduction in the change in BP but reported the change with 95% confidence intervals (CI). For severity of postural lightheadedness, dizziness or presyncope, quality of life or overall well-being, functionality, and overall orthostatic symptoms, we accepted study definitions of minimum important difference when validated scales were used. When unvalidated measurements were used, we considered a 10%

improvement as the minimum important difference. For change in frequency of postural lightheadedness, dizziness or presyncope, syncope, and falling, we considered a reduction of one event per week as the minimum important difference. For adverse events, we considered a statistically significant reduction in the likelihood of an event occurring as an important difference. We accepted any form of data aggregation (including but not limited to: median, mean or percentage of participants meeting a certain target).

Primary outcomes

- BP outcomes: change between pre- and post-treatment systolic BP and diastolic BP in the upright (standing or tilt) position, two to three minutes after standing or tilting was our preferred BP measurement after at least three weeks of treatment. However, we accepted any BP measurement method, including the pre- to post-treatment change in the drop in systolic BP and diastolic BP after moving from supine to upright, or from sitting to upright, and measurements taken outside the two to three minute range (that is, any time between one and five minutes).

Secondary outcomes

- Change in frequency and severity of postural lightheadedness, dizziness, or presyncope between pre- and post-treatment, measured as number of events per week (frequency) and with a validated tool or other measurement (severity)
- Change in frequency of syncope between pre-and post-treatment, measured as number of events per week
- Change in frequency of falling between pre- and post-treatment, measured as number of events per week
- Change in quality of life or overall well-being between pre- and post-treatment, measured with a validated scale (e.g. 36-item or 12-item Short Form Health Survey (SF-36 or SF-12), EuroQol five dimensions questionnaire (EQ-5D), Clinical Global Impression rating scale (CGI), Patient Global Impression of Change (PGIC)) or other measurement
- Change in functionality between pre- and post-treatment, measured with a validated scale or other measurement
- Change in overall orthostatic symptoms between pre- and post-treatment measured with a validated scale (e.g. Composite Autonomic Symptom Scale-Orthostatic Domain (COMPASS-OD)) or other similar measurement
- Adverse events due to treatment, regardless of association to treatment. We analyzed categories of: all adverse events, severe or serious adverse events that lead to hospitalization or death, and adverse events leading to cessation of treatment.

Search methods for identification of studies

Electronic searches

We searched the following databases on 11 November 2019.

- Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies (CRS-Web; Appendix 1).
- Cochrane Central Register of Controlled Trials (CENTRAL) via CRS-Web (Appendix 2).
- MEDLINE Ovid (1946 to November 2019; Appendix 3).
- Embase Ovid (1974 to November 2019; Appendix 4).
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to November 2019; Appendix 5).

We also searched MEDLINE and CENTRAL on 30 October 2017 (search strategies available in Appendix 6).

Searching other resources

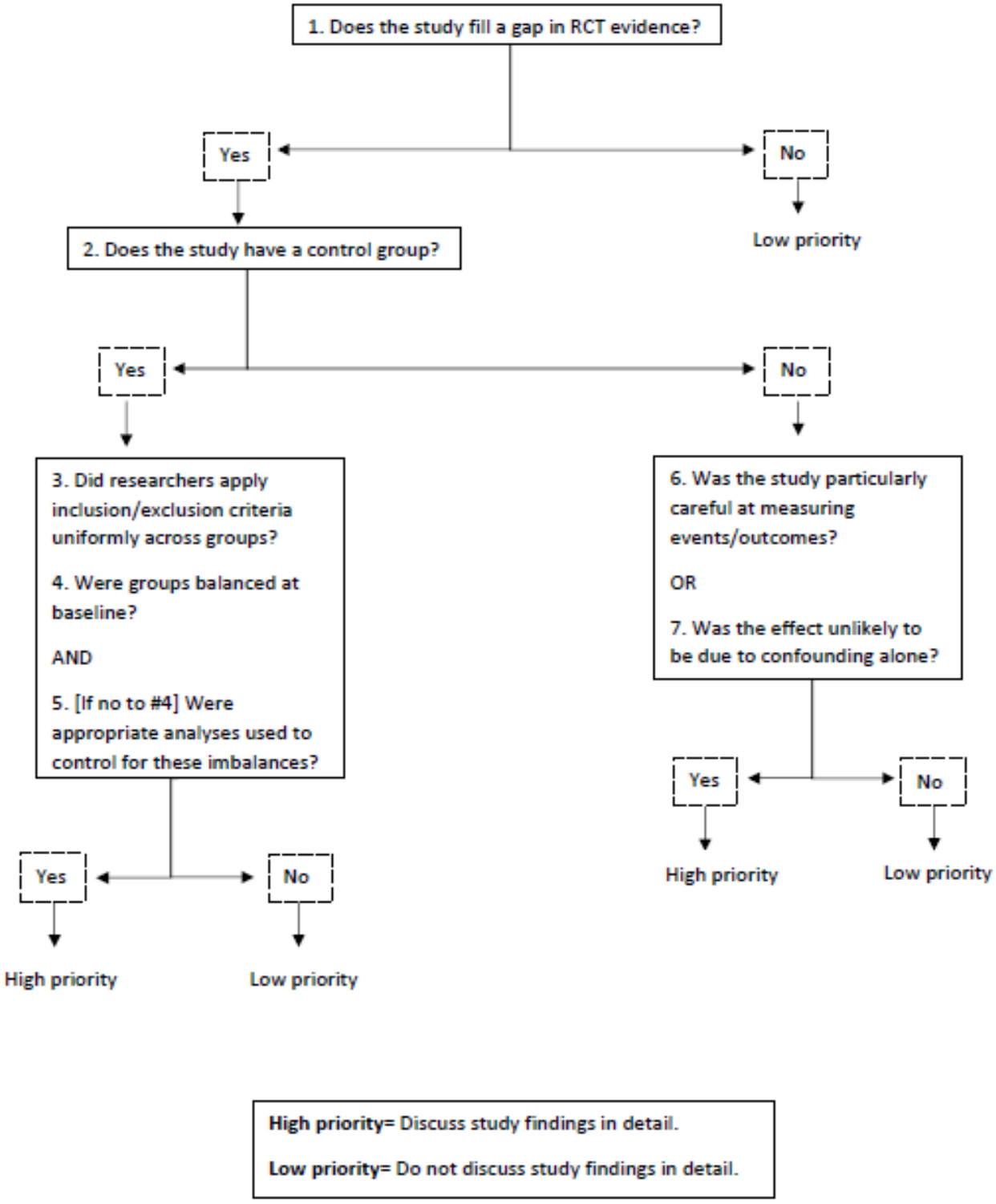
We searched US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov); the World Health Organization International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch); and the ISRCTN registry (www.isrctn.com) on 23 September 2019. We also reviewed the bibliographies of the relevant RCTs and non-randomized studies identified as well as relevant textbooks. We contacted known experts in the field.

Data collection and analysis

Selection of studies

Two review authors, including one clinician (YA or KAC) and one methodologist (KP or SV), independently reviewed titles and abstracts retrieved by the searches to identify relevant articles using the eligibility criteria described above. We retrieved full-text articles of potentially relevant citations and both reviewers independently assessed them for inclusion. If there was disagreement, a third review author (MH, CHG, or SRR) adjudicated. There were no language restrictions and we translated non-English articles into English as needed. We developed and used the Portland Observational Study Screening Tool for Interventions (POST-I) (Figure 1) to identify observational studies that offered the best evidence (Veazie 2019).

Figure 1. Portland Observational Study Screening Tool for Interventions (POST-I)



Data extraction and management

Two review authors, including one clinician (YA or KAC) and one methodologist (KP or SV), independently extracted data on population characteristics using a data extraction form that had been piloted. We gathered information on interventions, comparators, participant characteristics, outcomes, follow-up durations, settings, study design, eligibility criteria, conflicts of interest and funding. If there was disagreement, a third review

author (MH, CHG, or SRR) adjudicated. We only extracted data from the studies selected as above. One author (SV) entered 'Characteristics of studies' data into Review Manager (RevMan 2020).

Assessment of risk of bias in included studies

Two review authors, including one clinician (YA or KAC) and one methodologist (KP or SV), independently assessed risk of bias of selected studies according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (hereafter referred to as the *Cochrane Handbook;* Higgins 2017). For RCTs, we addressed the following domains as described in the *Cochrane Handbook*: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. For non-randomized studies, we used the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) assessment tool to assess bias due to confounding, participant selection, classification of interventions, deviation from intended interventions, missing data, outcome measurement and reporting of results (Sterne 2016). Key confounders included: disease state; severity of underlying illness; and presence of cardiac disease, smoking, diabetes or other co-morbidities. Relevant co-interventions included both non-pharmacological interventions (such as wearing compression socks, maintaining hydration, sleeping with the head elevated, and behavioural changes such as rising slowly) and pharmacological interventions (such as direct or indirect sympathomimetic pressor agents). If there was disagreement about judgments of risk of bias, a third review author (MH, CHG or SRR) adjudicated.

Measures of treatment effect

We analyzed all the primary and secondary outcomes under consideration. Because we did not identify two sufficiently similar studies, we did not undertake any meta-analysis in this version of the review. We used our clinical and methodological expertise when examining included studies' populations, interventions, comparators and outcomes to determine if studies were adequately homogeneous. See Appendix 7 for details of our planned meta-analyses from our protocol.

Unit of analysis issues

The unit of analysis was the participant. For RCTs we took into account both the level at which randomization occurred, and the trial design, such as cross-over trials, cluster-randomized trials and multiple observations for the same outcome. For cross-over trials, we preferred results from the first randomization period when available. For cluster-randomized trials, we only included data from those studies that used statistical methods that correctly account for the clustering in the data. For studies with multiple observations of the same outcome, we included all time points. We intended to conduct separate meta-analyses for each intervention-comparator pair of interest if at least two adequately homogeneous studies were identified.

Dealing with missing data

In the case of missing data that we could identify, we requested data from study authors. We analyzed the potential impact of missing data as part of the 'Risk of bias' assessment in included studies.

Assessment of heterogeneity

Because we did not identify sufficiently similar data to compare, we did not formally assess heterogeneity using the Chi^2 test and I^2 statistic (Higgins 2003).

Assessment of reporting biases

Because we did not identify sufficiently similar data to create a funnel plot, we did not formally assess reporting bias.

Data synthesis

Because we did not identify sufficiently similar studies to compare, we did not combine data from included RCTs in meta-analyses. We thus used a narrative synthesis approach to review the literature. We grouped results by population groups, and organized findings so that evidence from the studies with the highest certainty of evidence appears first. In the review, for each population group, we first described findings from RCTs, then we described results from NRSs that offered the best available evidence. Then we briefly described the studies that do not provide the best evidence, including the reason why.

Subgroup analysis and investigation of heterogeneity

Because we had insufficient data on subgroups, we did not conduct formal subgroup analyses.

Sensitivity analysis

Because we identified such limited evidence, we did not perform formal sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

Two review authors, including one clinician (YA or KAC) and one methodologist (KP or SV), independently rated the certainty of the evidence for the important outcomes across studies according to the GRADE approach, which considers risk of bias (study limitations), consistency, precision, directness, and reporting bias as criteria for downgrading the evidence, and a large magnitude of effect, dose response, and the effect of all possible confounding would be to reduce the effect, as criteria for upgrading the evidence (GRADEPro GDT). We justified all decisions to downgrade or upgrade the certainty of evidence using footnotes and we made comments to aid the reader's understanding of the review where necessary. If there was disagreement, a third review author (MH, CHG, or SRR) adjudicated.

We summarized strength of evidence ratings in a 'Summary of findings' table using GRADEpro GDT software. The 'Summary of findings' table includes the following outcome measurements for our primary comparison of interest (fludrocortisone versus placebo).

- BP outcomes: change in systolic BP and diastolic BP between pre- and post-treatment, as measured in the upright (standing or tilt) position, two to three minutes after standing/tilting.
- Change in frequency and severity of postural lightheadedness, dizziness or presyncope between pre- and post-treatment, measured as number of events per week (frequency) and through a validated scale (severity).
- Change in frequency of syncope between pre- and post-treatment, measured as number of events per week.

- Change in quality of life or overall well-being between pre- and post-treatment, measured through validated scales (e.g. SF-36 or SF-12, EQ-5D, CGI, or PGIC).
- Change in overall orthostatic symptoms between pre- and post-treatment using a validated scale (e.g. COMPASS-OD) or other similar measurement.
- Serious or severe adverse events due to treatment.

We included a 'Summary of findings' table for the comparison of fludrocortisone versus placebo.

RESULTS

Description of studies

Results of the search

Our searches in the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, CINAHL, and clinical trials registries identified 3004 records. From the 2535 studies remaining after removal of duplicates, we excluded an additional 2411 during title and abstract screening. After screening the full text of the remaining 124 studies, we excluded 111 (see Excluded studies for reasons for exclusion). We included 13 studies of 513 participants (three cross-over RCTs (Campbell 1975; Schoffer 2007; Schreglmann 2017), three cohort studies (Axelrod 2005; Pathak 2005a; Pathak 2005b), six case series (Campbell 1976; Chobanian 1979; Kochar 1978; Matsubara 1990; Schatz 1976; Ten Harkel 1992) and one case-control study (Axelrod 1997)).

The three RCTs (Campbell 1975; Schoffer 2007; Schreglmann 2017), one cohort study (Axelrod 2005) and one case series (Ten Harkel 1992) offer the best evidence (see Appendix 8 for details on why these five studies were selected). Specifically, we included and discussed these two observational studies in detail as they met the POST-I criteria and addressed gaps in RCT evidence by examining long-term outcomes. A flow diagram summarizing the study selection process is shown in Figure 2.

Figure 2.

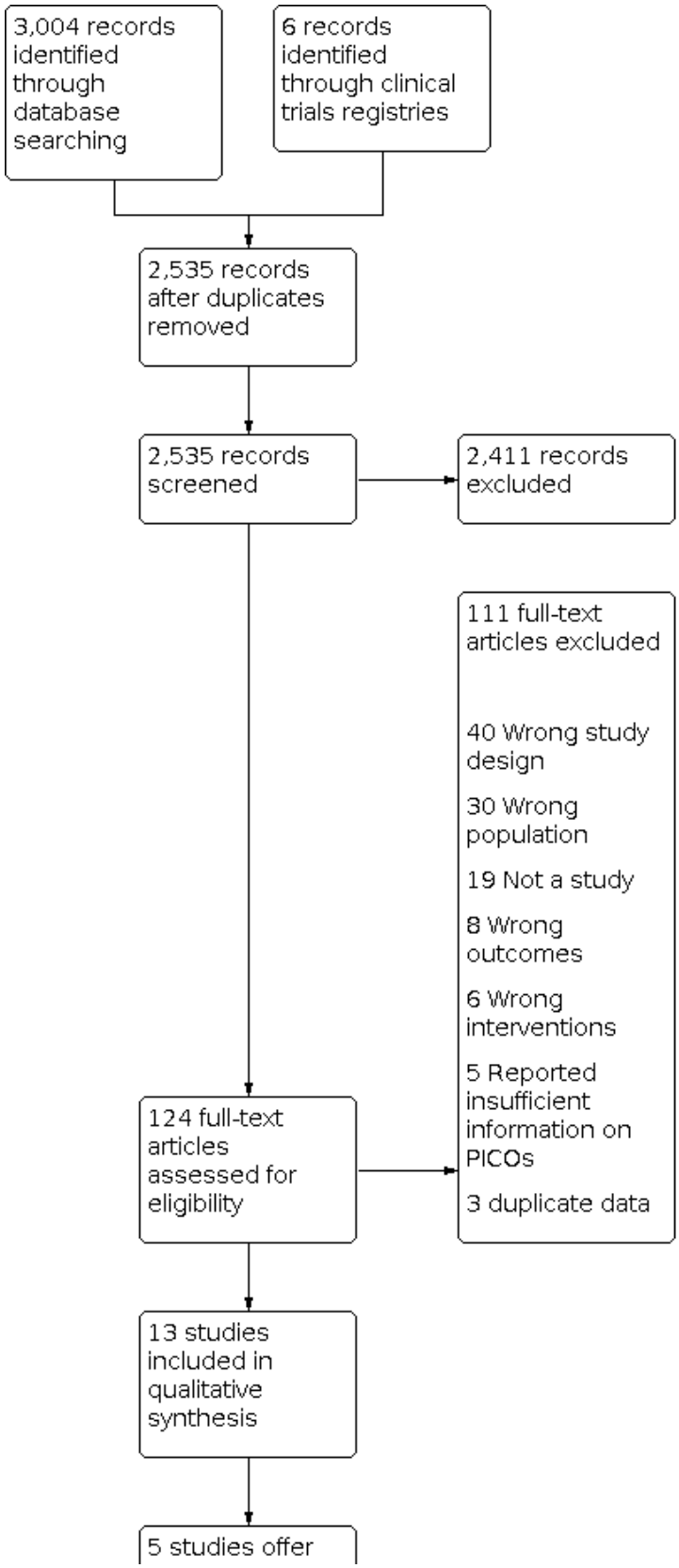
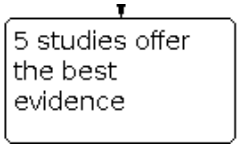


Figure 2. (Continued)



Included studies

We included 13 studies, of which only three were RCTs. We considered two more worthy of inclusion using the POST-I tool. We 'de-prioritized' eight studies, and we have not presented the data from these studies in the results apart from a brief description below.

Among our 13 studies, study size varied from five participants (in Kochar 1978) to 341 participants (in Axelrod 2005). Two studies were conducted in people with diabetes (Campbell 1975; Campbell 1976), two in those with Parkinson disease (Schoffer 2007; Schreglmann 2017), two in those with familial dysautonomia (Axelrod 1997; Axelrod 2005), one in those with Shy-Drager syndrome (Matsubara 1990) and six included multiple conditions including idiopathic orthostatic hypotension (Chobanian 1979; Kochar 1978; Pathak 2005a; Pathak 2005b; Schatz 1976; Ten Harkel 1992). All studies had a mix of men and women (range: 14% to 86% male), except for one study that only included men (Campbell 1975).

Five studies were conducted in the USA (Axelrod 1997; Axelrod 2005; Chobanian 1979; Kochar 1978; Schatz 1976), two studies in the UK (Campbell 1975; Campbell 1976), one in the Netherlands (Ten Harkel 1992), one in Switzerland (Schreglmann 2017), two in France (Pathak 2005a; Pathak 2005b), one in Australia (Schoffer 2007) and one in Japan (Matsubara 1990). Only two studies reported on the participants' race or ethnicity: in one, 80% of participants were white (Kochar 1978), and in another, 100% of participants were Ashkenazi Jewish (Axelrod 1997). Four studies were conducted in specialized clinics, those being for dysautonomia (Axelrod 1997; Axelrod 2005), diabetes (Campbell 1975), or movement disorders (Schoffer 2007). Four were conducted in outpatient settings (Campbell 1976; Pathak 2005a; Pathak 2005b; Schreglmann 2017), one was conducted in both hospital and outpatient settings (Ten Harkel 1992), three were conducted in research hospitals (Chobanian 1979; Kochar 1978; Schatz 1976), and one did not report the setting (Matsubara 1990).

Studies generally did not comment on comorbidities such as smoking and cardiac disease, although two commented that they excluded people with cardiac disease or who were on antihypertensive medications (Campbell 1975; Schreglmann 2017). One study compared fludrocortisone to placebo (Campbell 1975). Eight compared fludrocortisone to another treatment (midodrine (Axelrod 1997), domperidone (Schoffer 2007), pyridostigmine (Schreglmann 2017), indometacin (Kochar 1978), L-threo-3,4-dihydroxyphenylserine (Matsubara 1990), or compared fludrocortisone to multiple treatments (Axelrod 2005; Pathak 2005a; Pathak 2005b)). Four were observational studies of fludrocortisone alone (Campbell 1976; Chobanian 1979; Schatz 1976; Ten Harkel 1992). Six studies did not report or reported incomplete details on the regimen of fludrocortisone treatments (Axelrod 2005; Chobanian 1979; Kochar 1978; Pathak 2005a; Pathak 2005b; Schatz 1976). Among studies that did report regimen details on fludrocortisone treatments, the dosage ranged from 0.1 mg to 1.0 mg, administered once to three times daily. All but two studies measured BP (Pathak 2005b; Pathak 2005a), although a range of timings for measurements were used (for example one, three, five or 10 minutes after moving from supine to standing or tilting) and all but three studies measured or commented on orthostatic symptoms (Axelrod 2005; Campbell 1975; Campbell 1976; Chobanian 1979; Kochar 1978; Pathak 2005b; Schoffer 2007; Schreglmann 2017; Ten Harkel 1992). Four studies measured or commented on serious adverse events or survival (Axelrod 2005; Campbell 1976; Pathak 2005a; Pathak 2005b). Additional details of the five included studies that provide the best evidence are available in the Characteristics of included studies section. We have provided basic information on the eight studies that were de-prioritized in Appendix 9.

Excluded studies

Details of excluded studies are available in the Characteristics of excluded studies tables. The reasons for exclusion were:

- wrong design (40);
- not a study (19);
- wrong population (30);
- wrong intervention (6);
- no relevant data (8);
- reported insufficient information on PICOs (5); and
- duplicate data (3).

Risk of bias in included studies

Studies varied in terms of risk of bias. Among the three RCTs, one was at low risk of bias (Schreglmann 2017), and two were at unclear risk of bias (Campbell 1975; Schoffer 2007). Of the two observational studies that provided the best evidence, both were at high risk of bias (Axelrod 2005; Ten Harkel 1992). The primary methodological limitations of the RCTs were a lack of reporting of randomization, allocation and blinding procedures, as well as high overall attrition rates or differential attrition rates between groups.

The two observational studies were at high risk of bias because of their methodology in a number of areas. The primary methodological limitation of the observational studies was inadequate reporting on all important confounders. Detailed risk of bias ratings for prioritized studies are presented in the Characteristics of included studies section.

Allocation

All three RCTs were cross-over design, meaning each participant received both treatments and, therefore, there were no baseline differences between groups that could have affected results. However, the RCTs were variable in terms of whether they adequately described how random sequences were generated and how allocation was concealed (Campbell 1975; Schoffer 2007;

Schreglmann 2017). Bias could have been introduced if participants knew which drug they received during each phase of the study. As a result, the risk of bias due to randomization and allocation procedures ranged between low and unclear for these three studies.

Blinding

Among the RCTs, the risk of bias due to measurement of outcomes was low for objective outcomes such as BP measurements but unclear for subjective outcomes such as orthostatic symptoms (Campbell 1975). An exception to this was when the treatment arm was masked and dummy capsules were used for fludrocortisone and controls to maintain masking, as we felt this adequately controlled for this area of bias (Schoffer 2007; Schreglmann 2017).

Incomplete outcome data

The risk of bias due to incomplete outcome data ranged from low (Schoffer 2007; Schreglmann 2017) to unclear (Campbell 1975) among RCTs. Attrition was between 16% to 24% (Campbell 1975; Schoffer 2007; Schreglmann 2017).

Selective reporting

The risk of bias due to selection of reported results was unclear for two RCTs that did not have protocols (Campbell 1975; Schoffer 2007), and low for the last RCT, which did have a protocol (Schreglmann 2017).

Other potential sources of bias

First period data for Campbell 1975 were not available and there was no assessment for period effect. We identified no other potential sources of bias in Schoffer 2007 or Schreglmann 2017.

Risk of bias in non-randomized controlled trials

Bias in selection of participants

In the two observational studies (Axelrod 2005; Ten Harkel 1992), clinicians prescribed treatments based on clinical judgment. These decisions were likely influenced by participant characteristics, such as disease severity, that could have affected the likelihood of treatment success. In addition, in one study (Axelrod 2005), the sample was prevalent users, not new users, of fludrocortisone. The risk of bias due to selection bias is therefore high for these two observational studies.

Bias in classification of interventions

The risk of bias due to classification of interventions was low among the observational studies as either the intervention was well described (Ten Harkel 1992), or was appropriately ascertained from an international database which drew from annual examinations of participants (Axelrod 2005).

Bias due to departure from intended interventions

The risk of bias due to departure from intended interventions was low in Axelrod 2005 and unclear in Ten Harkel 1992.

Bias due to measurement of outcomes

Among the observational studies, the risk of bias due to measurement of outcomes was low for survival outcomes (Axelrod 2005) but unclear for other types of outcomes (Ten Harkel 1992).

Bias due to confounding

The observational studies were at unclear risk of bias due to confounding, as there was either no information about or control of key confounders (Axelrod 2005; Ten Harkel 1992).

Bias due to missing data

In one observational study (Axelrod 2005), analyses likely excluded 37% of data (high risk of bias) and in another (Ten Harkel 1992), all outcome data were likely included.

Bias due to selection of reported results

For one observational study, the risk of bias due to selection of reported results was high as analyses were retrospective and could have been the results of multiple analyses (Ten Harkel 1992), while the other was low as it only looked at a prespecified survival outcome (Axelrod 2005).

Effects of interventions

See: **Summary of findings 1** Fludrocortisone compared to placebo for people with diabetes and orthostatic hypotension

Diabetes

Fludrocortisone versus placebo in people with diabetes

Campbell 1975 investigated short-term use of fludrocortisone 0.2 mg compared to placebo in a three-week cross-over RCT of six people with diabetic neuropathy and symptomatic orthostatic hypotension. Our certainty in the findings is very low as they are supported only by a single, very small RCT with important methodological weaknesses. See Summary of findings 1 for full details on outcomes.

Primary outcome: BP outcomes

We found very low-certainty evidence about the effects of fludrocortisone on drop in BP in people with diabetes. Campbell 1975, three weeks after initiating treatment, reported mean systolic BP for fludrocortisone versus placebo while lying (180 mmHg versus 149 mmHg; $P < 0.05$, exact P value not reported) and tilted (154 mmHg versus 110 mmHg; $P < 0.005$, exact P value not reported), and mean diastolic BP while tilted (88 mmHg versus 76 mmHg; $P < 0.05$, exact P value not reported). The trial also reported data for fludrocortisone versus placebo on mean drop in BP when moving from lying to tilt (−26 mmHg versus −39 mmHg systolic; −7 mmHg versus −11 mmHg diastolic; 6 participants; very low-certainty evidence).

Secondary outcomes: postural lightheadedness, syncope, falling, quality of life, functionality, orthostatic symptoms, adverse events

For orthostatic symptoms, we found very low-certainty evidence for fludrocortisone versus placebo in people with diabetes. Four out of five participants who completed the study reported improvements in symptoms of orthostatic hypotension while on fludrocortisone, although these symptoms were not well described.

Fludrocortisone was associated with peripheral edema in two participants with hypoalbuminemia as well as a trend towards decreased potassium, but no side effects in the other three participants were reported. The study authors did not measure outcomes of quality of life or functionality.

Parkinson disease and related disorders

Clinically meaningful evidence is lacking about the comparative effectiveness of fludrocortisone to manage orthostatic hypotension in people with Parkinson disease. This is primarily because studies compared fludrocortisone to alternatives that are infrequently used in practice; namely, pyridostigmine and domperidone. Thus, the two available RCTs provide information that is not directly relevant to everyday practice (Schoffer 2007; Schreglmann 2017). Additionally, the accuracy and stability of the findings from these studies are questionable because the studies are so small (total N = 22) and short term (two to three weeks). Because no studies compared fludrocortisone to placebo in this population group, we did not include a 'Summary of findings' table for this population, but the evidence is of very low certainty because of multiple GRADE concerns, including very serious indirectness and imprecision.

One two-week cross-over RCT tested 0.1 mg of fludrocortisone for one day then 0.2 mg for 11 days versus 30 mg of pyridostigmine for three days then 60 mg for 11 days in nine people (Schreglmann 2017). Schreglmann 2017 reported the mean diastolic BP drop from supine to standing at two weeks for fludrocortisone versus pyridostigmine (-14 mmHg versus -22.1 mmHg; P = 0.036), but neither treatment was associated with improvements in overall orthostatic symptoms as measured through the Orthostatic Hypotension Daily Activities Scale (OHDAS) or Orthostatic Hypotension Severity Assessment (OHSA).

The other cross-over RCT tested 0.1 mg of fludrocortisone compared to 10 mg of domperidone in 13 people for three weeks (Schoffer 2007). It reported that neither domperidone nor fludrocortisone were associated with improvements in drop in systolic BP or diastolic BP from baseline, but both were associated with improved symptoms of orthostatic hypotension (Composite Global Impression of Change) (improvement to 1 for both); and the orthostatic domain of the Composite Autonomic Symptom Scale (COMPASS-OD) (improvement to 6 for both). Side effects were minimal in both studies: neither of the two studies detected hypokalemia, and one detected supine hypertension (Schreglmann 2017).

Familial dysautonomia

We found no RCTs of fludrocortisone in people with familial dysautonomia, but did find one cohort study (Axelrod 2005), and one case-control study (Axelrod 1997). We included Axelrod 2005 as it currently fills a gap in the evidence. We de-prioritized Axelrod 1997 as it was lower in the hierarchy and will be included in the discussion.

When fludrocortisone use in familial dysautonomia was compared to those who had never taken it, fludrocortisone was associated with better survival time (median 32.8 years versus 22.2 years), improved mean supine systolic BP and standing systolic BP after initiating treatment (98 mmHg versus 117 mmHg supine BP; 77 mmHg versus 64 mmHg standing BP at five minutes) and reduced dizziness, in a large retrospective registry study of 341 people with familial dysautonomia (Axelrod 2005). Fludrocortisone was not associated with improvement in syncope (syncope recurred in 38% of people on fludrocortisone who had syncope prior to the study, and 19% of those who did not have syncope prior to the study developed it). However, important limitations of these findings include that information was lacking on baseline severity of disease and whether there were differences in severity between treatment groups that may have confounded the effects of fludrocortisone. Because no studies compared fludrocortisone to placebo in this population group, we did not include a 'Summary of findings' table for fludrocortisone compared to placebo for people with familial dysautonomia.

Axelrod 2005 included participants with a mean standing BP lower than 60 mmHg, or the presence of syncope or presyncope, or both. The intent of the study was to examine the effects of fludrocortisone on mortality and other long-term outcomes associated with familial dysautonomia. The strengths of this study are its large sample size (N = 341), long follow-up period (nearly 40 years), and careful analysis methods. Overall, we trust the estimates on survival but are less certain about the estimates on BP change in this study. As an outcome, survival is less likely to be affected by biases in study design than BP. The authors of Axelrod 2005 were also more careful about how they measured and calculated survival than BP. For example, authors did not report the mean time from initiation of treatment at which BP drop was measured, making it difficult to determine the applicability of the results. However, it should be noted that both outcomes were at risk of confounding bias, as authors acknowledge that assignment to the fludrocortisone group was likely based on clinical characteristics such as symptom severity.

Studies in people with various forms of orthostatic hypotension

Five studies included a variety of participants with different forms of orthostatic hypotension, including Parkinson disease, pure autonomic failure, MSA, Lewy body disease, secondary diabetic and nondiabetic peripheral neuropathies, autonomic failure, undifferentiated nervous system disease and amyloidosis (Chobanian 1979; Pathak 2005a; Pathak 2005b; Schatz 1976; Ten Harkel 1992). We included Ten Harkel 1992 as it currently fills a gap in evidence, but we de-prioritized the remaining four studies as they were lower in the hierarchy (Chobanian 1979; Pathak 2005a; Pathak 2005b; Schatz 1976). We discuss these studies in the Discussion.

Ten Harkel 1992 is a case series that reported that fludrocortisone increased standing BP both acutely (increase from 58/42 mmHg to 95/57 mmHg) and in long-term follow-up (99/63 mmHg) (mean of 14 months, range 8 to 70 months). Participants in this study experienced some ankle edema and hypokalemia but otherwise no serious long-term harms.

DISCUSSION

Summary of main results

Our review identified little useful, and no high certainty, evidence for evaluating the benefits and harms of fludrocortisone for orthostatic hypotension. Randomized controlled trials (RCTs) were few (N = 3; Campbell 1975; Schoffer 2007; Schreglmann 2017), very small (28 participants in total) and short term (two to three weeks). Use of meta-analysis to combine data across trials was not possible because of heterogeneity in participant populations, comparators and outcome assessment methods.

The evidence about the effects of fludrocortisone on BP drop and orthostatic symptoms compared to placebo in people with diabetes, and to pyridostigmine and domperidone in people with

Parkinson disease was very uncertain. The evidence from these trials on adverse events of fludrocortisone is also very uncertain.

A hypothetical concern for the use of mineralocorticoids is risk of hypokalemia. In one RCT, fludrocortisone was associated with peripheral edema in two people with hypoalbuminemia as well as a trend towards decreased potassium, but no other unusual side effects (Campbell 1975). Neither of the two studies conducted in people with Parkinson disease detected hypokalemia. Supine hypertension is another potential unintended side effect of treatment. While supine hypertension is harder to define, a significant increase in supine systolic BP was noted in two of three studies (Campbell 1975; Schreglmann 2017). Overall, however, adverse events were tolerable.

Because of gaps in RCT evidence, we also included two observational studies in our results. Among those, the most useful information came from one large cohort study that partially filled the RCT gap in evidence by examining the long-term effects (nearly 40 years) of fludrocortisone in people with familial dysautonomia (Axelrod 2005). Findings from this study indicate that fludrocortisone may not be harmful in the long term for some rare population groups. However, it is unclear if this translates to long-term improvements in BP drop or a meaningful improvement in orthostatic symptoms. Because this study did not report baseline disease severity or confounders, we cannot conclude that fludrocortisone is associated with long-term improvements in BP or orthostatic symptoms. However, we can conclude that fludrocortisone may not be harmful to people with familial dysautonomia, as survival was better in those who received fludrocortisone than those who did not. Study authors noted that those who received fludrocortisone had more long-term problems, which could be due to confounding, as these people were living longer and may naturally have more health problems as they age. Another small case series that followed a mixed population of people with orthostatic hypotension over an average of 14 months found minor side effects of fludrocortisone, including ankle edema and hypokalemia, but no other serious events (Ten Harkel 1992), supporting our conclusion that fludrocortisone is may not be harmful in the long term.

Additional evidence from de-prioritized studies

Diabetes

For the use of fludrocortisone in diabetic orthostatic hypotension, one very small RCT provided very low certainty evidence of a short-term benefit but offered no long-term data (Campbell 1975).

In one de-prioritized case series of 14 people with diabetes and symptomatic hypotension, initial treatment of 0.1 mg of fludrocortisone for a mean of 12 months (range: 6 to 30 months) was associated with increased standing systolic BP and diastolic BP, as well as decreased BP drop, but no increase in supine BP (Campbell 1976). The study also reported that 13 out of 14 participants noted an improvement in symptoms. However, this study had major methodological limitations, including insufficient information about participants' baseline characteristics and stability of other potential conditions, or treatments to rule out potential sources of important confounding, or both.

Movement disorders

The two RCTs exploring orthostatic hypotension in Parkinson disease were very limited, as above.

There are no RCTs or high quality evidence for the use of fludrocortisone in multiple system atrophy (MSA). The evidence is limited to two small, de-prioritized studies (total N = 13) that lacked concurrent comparison groups and adequate control for important confounding due to participant-level and temporal trend factors (Kochar 1978; Matsubara 1990). On the fourth day of treatment in four people with MSA, fludrocortisone was associated with increased systolic BP and diastolic BP and symptom improvement in two participants, while indomethacin was associated with improvements for all four participants (Kochar 1978). In nine people with MSA, two weeks of fludrocortisone was associated with improvements in BP drop and L-DOPS (droxidopa) was associated with improvements in both BP drop and cerebral blood flow when moving from supine to sitting (Matsubara 1990).

Familial dysautonomia

While Axelrod 2005 provided some data on the possible effect of fludrocortisone on survival, Axelrod 1997 was de-prioritized as it fell lower in the evidence hierarchy. This study compared 10 participants with familial dysautonomia to eight healthy control participants on measures of BP, heart rate, and corrected QT Interval (QTc) to determine if autonomic dysfunction involved peripheral vascular integrity in addition to cardiac integrity (Axelrod 1997). One hour after receiving fludrocortisone, participants with familial dysautonomia had decreased mean BP in both supine and tilt position, while one hour after receiving midodrine, participants had increased supine BP and decreased tilt BP. A strength of Axelrod 1997 is that it provides the only evidence about the most relevant comparison of fludrocortisone versus midodrine. However, it is very short term and reported baseline differences between intervention groups that were not adequately controlled for in analyses. Therefore, the findings of Axelrod 1997 should be considered very low certainty.

Various forms of orthostatic hypotension

One case series provided limited information on long-term harms of fludrocortisone among those with orthostatic hypotension due to a variety of conditions (Ten Harkel 1992). Four additional, de-prioritized studies provide additional data on populations with a range of different conditions and orthostatic hypotension (Chobanian 1979; Pathak 2005a; Pathak 2005b; Schatz 1976). Two are cohort studies (Pathak 2005a; Pathak 2005b), and two are case series (Chobanian 1979; Schatz 1976).

One case series found fludrocortisone increased standing BP in the short term and long term (Chobanian 1979), which aligns with findings from Ten Harkel 1992. A second case series found that fludrocortisone was tolerable for most (18/23) participants with a range of conditions causing orthostatic hypotension (Schatz 1976). Five participants, however, discontinued their treatment due to either recumbent hypertension (N = 4) or congestive heart failure (N = 1). We de-prioritized these studies as researchers were not particularly careful at measuring outcomes and we could not rule out the possibility that effects were due to confounding.

Additionally, a prospective study of 121 people that had a primary objective of systematically evaluating adverse drug reactions

found no significant differences between the frequency of adverse drug reactions in those taking midodrine alone, fludrocortisone alone, or combined treatment (Pathak 2005a). Findings from the other cohort study (N = 31) suggested that heat exposure is a risk factor for worsening orthostatic hypotension and that those taking fludrocortisone may have a higher risk of clinical events than those taking heptaminol, midodrine or combination therapy (Pathak 2005b). A strength of these cohort studies is that they had comparison groups. However, we de-prioritized them because they had baseline differences between intervention groups that were not controlled for in analyses.

Overall completeness and applicability of evidence

The best evidence on fludrocortisone is limited to those with diabetes, Parkinson disease, familial dysautonomia and those with a variety of conditions underlying orthostatic hypotension, with each supported by one or two studies. We only identified observational evidence for people with MSA, Lewy body disease or amyloid-induced orthostatic hypotension, which was too low certainty to warrant inclusion in the Results section of this review. The best evidence compared fludrocortisone to placebo, pyridostigmine, domperidone or no fludrocortisone treatment. None of these studies compared fludrocortisone to midodrine, which is typically considered either first- or second-line treatment for orthostatic hypotension. Studies also examined a limited number of outcomes - primarily some measurement of orthostatic BP (such as mean supine BP and standing BP, or mean drop when moving from supine to standing), some measurement of orthostatic or general symptoms (such as through the COMPASS-OD, OHSA, or CGI) and some measurement of side effects. No studies examined frequency of syncope, falling or quality of life. Studies generally were not long enough to detect serious adverse events, although one long-term observational study examined mortality (Axelrod 2005). Due to the heterogeneity in populations, comparators and outcomes, we did not have sufficient numbers of similar studies to conduct meta-analyses.

Given the limited available evidence on the efficacy of fludrocortisone treatment, particularly on long-term health outcomes, it may be surprising that fludrocortisone is considered first-line pharmacological treatment for orthostatic hypotension. However, the most promising alternative treatment (midodrine) has historically been associated with side effects, including supine hypertension, which can sometimes be serious (NICE 2013). Our review further iterates that fludrocortisone is likely not harmful in the long term for some patient groups, but we could not determine if it is effective long term for any patients.

Quality of the evidence

The certainty of the evidence is mixed and, in general, low or very low. The main limitations of the RCTs were small sample sizes (less than 15 participants), short duration (three weeks or less), insufficient detail to assess adequacy of randomization, allocation and masking procedures, as well as high overall attrition rates or differential attrition rates between groups, and clinically irrelevant comparator treatments. The main methodological limitation of the observational studies was not reporting or accounting for important confounders that may have influenced results. Additional limitations of the observational evidence include a lack of detailed information on fludrocortisone dosage or mixed dosages across participants, as well as a lack of measurement of patient-important outcomes.

Potential biases in the review process

We worked to reduce bias by applying a rigorous searching process (including searching multiple databases, trials registries, talking to experts and translating non-English articles into English) as well as a rigorous article selection process (one clinician and one methodologist reviewed each article for eligibility and resolved disagreements through consensus). Nevertheless, it is still possible we missed eligible studies. It is possible but unlikely that evidence has emerged since we searched for studies, as new studies are infrequent. We also worked to reduce bias in our selection of the best observational evidence by creating the POST-I screening tool that we could apply across studies. It is possible that other reviewers could have applied a different approach and selected different studies. However, it is likely that inclusion of the additional available observational studies would not meaningfully change our conclusions as the risk of bias was at best high due to use of inadequate methods for selecting participants and controlling for important confounding.

Agreements and disagreements with other studies or reviews

This review includes two RCTs (Campbell 1975; Schoffer 2007) also discussed in Ong 2013, the systematic review that formed the basis of the most recent NICE guidance (NICE 2013). The Ong 2013 review concluded that fludrocortisone and midodrine are associated with improvement in standing and head-up tilt BP but there is limited evidence of an improvement in other clinical outcomes. Although we cannot safely draw any conclusions, our review adds to the evidence by adding a recently published RCT that reported improvement with fludrocortisone on BP but not orthostatic symptoms in people with Parkinson disease (Schreglmann 2017), as well as the best observational evidence from two observational studies that indicate fludrocortisone may not be associated with long-term harms for people with familial dysautonomia or those with either diabetes or a variety of conditions underlying orthostatic hypotension (Axelrod 2005; Ten Harkel 1992).

AUTHORS' CONCLUSIONS

Implications for practice

The evidence is very uncertain about the effects of fludrocortisone on blood pressure drop, orthostatic symptoms or adverse events in people with orthostatic hypotension and diabetes or Parkinson disease. We still need larger and longer-term studies that compare fludrocortisone to midodrine, the most promising alternative treatment, on other important health outcomes.

Fludrocortisone is likely to continue to be considered one pharmacological treatment option for people with orthostatic hypotension in the short term. Clinicians should monitor patient progress to determine if an improvement in BP leads to an improvement in other outcomes, and look for potential side effects such as hypokalemia and supine hypertension. Long-term use should be accompanied by careful monitoring, as there is a paucity of data on long-term fludrocortisone use.

Implications for research

This review identified several research gaps. First, there is a need for RCTs evaluating the effects of fludrocortisone on conditions such as Lewy body disease, multiple system atrophy, amyloid-induced orthostatic hypotension and familial dysautonomia. None of these patient groups which have orthostatic hypotension were evaluated in RCTs, so we cannot say for certain if fludrocortisone is associated with an improvement in outcomes in these groups. Second, there is a need for a head-to-head RCT of fludrocortisone versus midodrine, as these represent pharmacological treatment options. Including a third placebo arm would help control for the expectancy effects associated with receiving treatment. Third, RCTs should assess the effect of fludrocortisone on other important patient outcomes such as syncope, falls and quality of life, as these outcomes are important to informing clinical decision-making. Fourth, RCTs of a longer duration (at least six months) are needed to see if short-term changes in BP drop correspond to longer-term changes in other outcomes. Fifth, observational studies should evaluate whether fludrocortisone is associated with adverse events when used for long periods of time for conditions other than familial dysautonomia. Sixth, observational studies should evaluate different clinical approaches to fludrocortisone (e.g. fludrocortisone administered as the initial pharmacological approach versus as a second or third approach if other treatments are unsuccessful). Seventh, observational studies should report on baseline disease severity and measure potential confounders, and RCTs should report randomization, allocation and masking procedures.

Lastly, there is a great need for more rigorous research and use of a standardized, core set of outcomes. Specifically, researchers may want to consider using a higher threshold of orthostatic hypotension for inclusion in research studies than they would use to diagnose people with orthostatic hypotension in practice. There are people that meet clinical criteria for orthostatic hypotension, but who do not require treatment. A higher threshold for orthostatic hypotension (e.g. 30/15 mmHg) would decrease the possibility of overtreatment.

More generally, studies of orthostatic hypotension should use a core set of outcome measures, including both objective and subjective outcomes measures. In terms of objective measures, we propose all authors report mean supine BP and mean standing or tilted BP at three minutes so that data can be combined across studies. For people with such severe orthostatic symptoms they cannot stand for three minutes, BP should be measured as long as they are able to stand or tilt. In addition, the use of real-world measurements such as ambulatory BP may provide useful information to clinical practice, although we acknowledge the technologies necessary to measure these outcomes can be expensive and are not always readily accessible.

Lastly, observational studies should report on baseline disease severity and measure potential confounders, and RCTs should report randomization, allocation and masking procedures.

The use of a core set of subjective measures in orthostatic hypotension is also important. One of the biggest challenges in studying orthostatic hypotension is that orthostatic symptoms are difficult to measure, as people with subtle cognitive symptoms can be unaware of symptoms, unable to describe them or misinterpret one as another (i.e. imbalance as dizziness). This makes it difficult to determine whether differences in symptoms over time are due to treatment, or are just being reported in different ways. The use of standardized measurements (versus asking about overall symptoms) are one way to counteract this challenge. It may be feasible to create these types of standardized measures for more common diseases such as Parkinson disease and diabetes, but more challenging for rare diseases such as familial dysautonomia, as it is challenging to recruit the numbers of participants necessary to validate a measure. Initiatives such as the USA-based Patient-Centered Outcomes Research Institute (PCORI) are starting to bringing together researchers working on patient-reported outcome (PRO) tools, including for rare diseases, for exactly this purpose, and may be a useful resource for researchers going forward. Another major challenge in studying orthostatic hypotension is that it is difficult to recruit sufficient numbers of participants into trials of orphan drug indications. Collaboration between centers may be one way to increase the number of participants in these trials (Schreglmann 2018), although we acknowledge this approach presents its own set of logistical challenges.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Axelrod 1997

Study characteristics	
Methods	See Appendix 9: Basic study characteristics of 8 de-prioritized studies
Participants	
Interventions	
Outcomes	
Notes	

Axelrod 2005

Study characteristics	
Methods	Retrospective analysis of US data from Familial Dysautonomia database
Participants	*Setting*: Dysautonomia Treatment and Evaluation Center at New York University Medical Center *Number of participants:* 341 *Group selection:* clinical decision to administer fludrocortisone or not *Age (mean):* 14.7 *Diagnostic criteria of orthostatic hypotension:* indication for fludrocortisone therapy included 1. supine or erect mean BP < 60 mmHg, 2. the presence of presyncope or syncope, or both 1 and 2. *Severity of orthostatic hypotension:* for fludrocortisone, drop of systolic BP 28 mmHg at 1 min, 34 mmHg at 5 min *Severity of underlying illness:* not reported *Inclusion/exclusion criteria:* met diagnostic criteria for Familial Dysautonomia and had information from annual examinations
Interventions	*Intervention/exposure:* fludrocortisone *Comparator:* no fludrocortisone
Outcomes	*Time points reported:* baseline, last recorded observation *Primary outcome:* mean systolic BP in supine and erect position (1 min and 5 min) *Secondary outcome:* dizziness, survival
Notes	Conflicts of interest not reported. Funding from Dysautonomia Foundation, Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection Bias	High risk	Assignment to fludrocortisone group was based on clinical characteristics such as symptom severity. Sample was prevalent users
Bias in measurement of interventions	Low risk	Worldwide Familial Dysautonomia database classification
Bias due to departure from intended interventions	Low risk	Worldwide Familial Dysautonomia database classification. Intent is to assess effect of assignment, not adherence. No reason to expect deviations due to departures from usual care
Bias due to measurement of outcomes	Low risk	No information about assessment methods, but differential misclassification less likely for survival outcome
Bias due to confounding	Unclear risk	No information about or control for key confounders
Bias due to missing data	Unclear risk	No information about completeness of data for survival. For systolic BP erect at 5 min, df = 109, which implies authors excluded 37% of data
Bias in the selection of reported results	Low risk	Survival analyzed both continuously and categorically. The 10-year categorization was prespecified

Campbell 1975

Study characteristics	
Methods	Cross-over RCT
Participants	*Setting:* Diabetic and Dietetic Department, University Department of Medicine, The Royal Infirmary, Edinburgh *Number of participants*: 6 *Unit of randomization*: individual *Age (mean):* 50 *Diagnostic criteria of orthostatic hypotension:* symptomatic postural hypotension with a fall of systolic BP of 30 mmHg or greater immediately on changing from the lying to standing position *Severity of OH:* see “diagnostic criteria of orthostatic hypotension” *Severity of underlying illness:* severe diabetic neuropathy *Inclusion/exclusion criteria:* see “diagnostic criteria of orthostatic hypotension”
Interventions	*Intervention:* 0.1 mg of fludrocortisone twice a day for 3 weeks *Comparator:* placebo twice a day for 3 weeks
Outcomes	*Time points reported:* baseline, 3 weeks *Primary outcome:* mean systolic and diastolic BP in lying and tilted position at 1-min increments *Secondary outcomes:* orthostatic symptoms
Notes	Conflicts of interest not reported. Fludrocortisone and placebo tablets were supplied by ER Squibb and Son, Ltd

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Low for BP; unclear for symptoms
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Low for BP; unclear for symptoms
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Low for BP; unclear for symptoms, 16% attrition while taking active drug for reason of "defaulted"

Campbell 1975 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	First period data not available. No assessment for period effect

Campbell 1976

Study characteristics	
Methods	See Appendix 9: Basic study characteristics of 8 de-prioritized studies
Participants	
Interventions	
Outcomes	
Notes	

Chobanian 1979

Study characteristics	
Methods	See Appendix 9: Basic study characteristics of 8 de-prioritized studies
Participants	
Interventions	
Outcomes	
Notes	

Kochar 1978

Study characteristics	
Methods	See Appendix 9: Basic study characteristics of 8 de-prioritized studies
Participants	
Interventions	
Outcomes	
Notes	

Matsubara 1990

Study characteristics	
Methods	See Appendix 9: Basic study characteristics of 8 de-prioritized studies
Participants	
Interventions	
Outcomes	
Notes	

Pathak 2005a

Study characteristics	
Methods	See Appendix 9: Basic study characteristics of 8 de-prioritized studies
Participants	
Interventions	
Outcomes	
Notes	

Pathak 2005b

Study characteristics	
Methods	See Appendix 9: Basic study characteristics of 8 de-prioritized studies
Participants	
Interventions	
Outcomes	
Notes	

Schatz 1976

Study characteristics	
Methods	See Appendix 9: Basic study characteristics of 8 de-prioritized studies
Participants	
Interventions	

Schatz 1976 *(Continued)*

Outcomes	
Notes	

Schoffer 2007

Study characteristics	
Methods	Double-blind, randomized, active-control, cross-over trial
Participants	*Setting:* 2 movement disorder clinics in Australia *Number of participants*: 17 *Unit of randomization*: individual *Age (mean):* 69.5 *Diagnostic criteria of orthostatic hypotension:* 20 mmHg drop in systolic BP, 10 mmHg drop in diastolic BP at baseline (but including people who met criteria at any prior time, as long as still symptomatic) *Severity of orthostatic hypotension:* at baseline, average maximum systolic drop over 5 min was 34 mmHg. Diastolic BP average maximum drop was 16 mmHg *Severity of underlying illness:* mean United Parkinson's Disease Rating Scale motor score of included participants was 25.5. *Inclusion criteria:* participants with diagnosis of idiopathic Parkinson disease; stable doses of medications for Parkinson disease. *Exclusion criteria*: participants with multiple system atrophy, acute coronary syndrome, inability to give informed consent, another cause of autonomic failure, systolic BP > 200 mmHg or diastolic BP > 100 mmHg
Interventions	*Intervention:* 0.1 mg of fludrocortisone once a day for 3 weeks *Comparator:* 10 mg domperidone 3 times a day for 3 weeks
Outcomes	*Time points reported:* baseline, 3 weeks *Primary outcome:* 1) Median maximum change in supine systolic BP and diastolic BP in the 5 min after a 5-min 80° head-up tilt. 2) Change in systolic BP and diastolic BP at 3 min. 3) Supine systolic BP *Secondary outcomes:* composite Global Impression of Change (CGI), composite Autonomic Symptom Scale-Orthostatic Domain (Compass-OD)
Notes	Conflicts of interest not reported. Funding not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization with "Research Randomizer”
Allocation concealment (selection bias)	Low risk	Dummy capsules to maintain blinding

Schoffer 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Dummy capsules to maintain blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Dummy capsules to maintain blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 13 participants reached drug treatment (4 withdrew from side effects)
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	No other bias identified

Schreglmann 2017

Study characteristics	
Methods	Double-blind, randomized, active-control, cross-over, phase II non-inferiority trial
Participants	*Setting:* outpatient clinics of participating centers *Number of participants*: 13 *Unit of randomization*: individual *Age (mean):* 71.3 *Diagnostic criteria of orthostatic hypotension:* ≥ 20 mmHg drop systolic or 10 mmHg diastolic peripheral BP within 3 min of standing on routine follow-up. *Severity of orthostatic hypotension:* average drop of 22.9 ± 12.6 mmHg *Severity of underlying illness:* mean United Parkinson's Disease Rating Scale of included participants 24.2 ± 8.6, Montreal Cognitive Assessment 23.9 ± 3.3, Parkinson's Disease Questionnaire 24.9 ± 18.6 *Inclusion/exclusion criteria:* Parkinson disease patients (using UK Brain Bank criteria) with symptomatic, established orthostatic hypotension were included. Patients on medication affecting BP regulation, systemic diseases such as diabetes, infection, renal or kidney failure, malignancy, with weight gain or loss or who were underweight or overweight, and those with multiple system atrophy were excluded
Interventions	*Intervention:* 0.1 mg of fludrocortisone once a day for 3 days then 0.2 mg for 11 days *Comparator:* 30 mg pyridostigmine bromide 3 times a day for 3 days then 60 mg for 11 days
Outcomes	*Time points reported:* 14 days duration with 21 days of wash out before crossover *Primary outcome:* mean systolic and diastolic BP when moving from supine to standing at 10 min *Secondary outcomes:* orthostatic symptoms (Orthostatic Hypotension Daily Activity Scale), subjective assessment of symptom severity

Schreglmann 2017 *(Continued)*

Notes	Authors report no conflicts of interest. Study supported by HSM-II initiative, Canton of Zurich and Parkinson Schweiz

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided
Allocation concealment (selection bias)	Low risk	Randomization performed by Cantonal Pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Drugs prepared in identical capsules at separate site
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Drugs prepared in identical capsules at separate site
Incomplete outcome data (attrition bias) All outcomes	Low risk	20% attrition, but the investigators have appropriate data analysis strategy to account for missing data
Selective reporting (reporting bias)	Low risk	Outcomes from ClinicalTrials.gov are reported
Other bias	Low risk	No other bias identified

Ten Harkel 1992

Study characteristics

Methods	Case series
Participants	*Setting*: hospital and outpatient at medical clinic *Number of participants:* 6 *Group selection:* 6 consecutive patients referred for evaluation of orthostatic hypotension were all given fludrocortisone *Age (mean):* 51.83 *Diagnostic criteria of orthostatic hypotension:* not reported *Severity of orthostatic hypotension:* severe (orthostatic hypotension was generally described as “incapacitating” or “progressive” over several years) *Severity of underlying illness:* not reported *Inclusion/exclusion criteria:* Hypoadrenergic orthostatic hypotension
Interventions	*Intervention/exposure:* 0.1 mg or 0.2 mg daily fludrocortisone with diet containing 150 mmol Na+ to 200 mmol Na+ and minimal water and sleeping in 12% head-up position

Ten Harkel 1992 *(Continued)*

	Comparator: diet and head-up sleeping position alone
Outcomes	*Time points reported:* baseline, weekly for 3 weeks and again at 14 months *Primary outcome:* standing BP and drop in BP *Secondary outcome:* orthostatic disability score, standing time
Notes	Conflicts of interest not reported. Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection Bias	High risk	Selection based on referral to academic center for evaluation, so this was not an inception cohort at the same point of their disease process
Bias in measurement of interventions	Low risk	Intervention groups clearly defined and not affected by knowledge of outcome
Bias due to departure from intended interventions	Unclear risk	No information on co-interventions or adherence
Bias due to measurement of outcomes	Unclear risk	No information on whether outcome assessors were aware of intervention, but measurement methods were well-described and objective
Bias due to confounding	Unclear risk	No information on potential confounders
Bias due to missing data	Low risk	Outcome data available for all participants
Bias in the selection of reported results	High risk	Effect estimates not prespecified and possible to generate multiple types based on measures collected

BP: blood pressure

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbruzzese 1981	Wrong study design
Agrawal 1999	Wrong study design
Ahmad 1990	Wrong study design
Andreelli 1999	Wrong study design
Anlauf 1975a	No relevant data
Anlauf 1975b	Duplicate data
Anonymous 1958	Wrong population
Bagatin 1995	Wrong study design
Ballabio 1956	Wrong population

Study	Reason for exclusion
Bannister 1969	No relevant data
Bannister 1979	Wrong study design
Barnett 1968	Wrong study design
Barnett 1976	Wrong study design
Bodemer 1986	Wrong study design
Bodemer 1987	No relevant data
Borck 1974	Wrong population
Bowen 1988	Wrong study design
Bradshaw 1986	Wrong study design
Brown 1968	Wrong study design
Castillo 1982	Wrong study design
Charlier 1980	Wrong study design
Chung 2016	Only title/abstract available and insufficient reporting on PICOs to determine eligibility
Cohen 1991	Wrong population
Colombat 1977	Only title/abstract available and insufficient reporting on PICOs to determine eligibility
Comi 1988	Wrong study design
Davidson 1976	Wrong study design
Davies 1978	Duplicate data
Davies 1979	No relevant data
Davies 1982	Wrong study design
Decaux 1979	Wrong study design
Decourt 1958	Wrong population
Degennes 1955	Wrong study design
Devuyst 1992	Wrong study design
Finke 1975	Wrong population
Fouad 1986	Wrong population
Freidenberg 2013	Wrong intervention

Study	Reason for exclusion
Frewin 1973	Wrong study design
Frick 1966	Wrong population
Goovaerts 1984	Wrong study design
Grijalva 2017	Wrong population
Hakamaki 1998	Wrong population
Hall 1961	Wrong population
Hamwi 1955	Wrong population
Hawkins 1982	Wrong study design
Herpin 1979	Not a study
Hickler 1959	Wrong study design
Hohl 1965	Wrong study design
Hohler 2012	Wrong intervention
Hussain 1996	Wrong population
Ibrahim 1975	Not a study
Irvin 1970	Wrong study design
Jay 2001	Wrong study design
Jorg 1983	Wrong study design
Khurana 1987	Wrong study design
Kochar 1977	Wrong intervention
Lange 1983	Not a study
Legeler 1971	Wrong population
Lennox 1980	Wrong population
Lewis 1972	Wrong intervention
Low 1978	Not a study
MacLean 1959	Wrong study design
Mathias 1998	Not a study
Maximilian 1977	Wrong population
Meijer 1977	Wrong study design

Study	Reason for exclusion
Miller 1976	Wrong population
Miskiewicz 1982	Wrong study design
Mittal 2007	Not a study
Molnar 1963	Wrong study design
NCT00103597	Duplicate data
Oldenburg 1999	Wrong study design
Perkins 1978	Wrong study design
Peterson 1998	Wrong population
Poppe 1980	Wrong intervention
Radian 1976	Only title/abstract available and insufficient reporting on PICOs to determine eligibility
Robertson 1979	No relevant data
Robertson 1985	Not a study
Salim 2005	Wrong population
Schafer 1957	Wrong study design
Schatz 1984	Not a study
Schatz 2001	Not a study
Schirger 1964	No relevant data
Schreglmann 2018	Not a study
Scott 1995	Wrong population
Seagar 1963	Wrong study design
Seller 1969	Wrong study design
Selye 1955	Wrong population
Selye 1956	Wrong population
Shear 1968	No relevant data
Shibao 2011	Only title/abstract available and insufficient reporting on PICOs to determine eligibility
Shibao 2013a	Only title/abstract available and insufficient reporting on PICOs to determine eligibility

Study	Reason for exclusion
Shibao 2013b	Wrong population
Silvestrini 1964	Wrong study design
Simoes 2018	Not a study
Sivertssen 1967	Not a study
Stoll 1971	Wrong population
Tantengco 1986	Not a study
Tarazi 1978	Not a study
Tifft 1985	Not a study
Vassallo 2013	Not a study
Villa 1955	Wrong population
Volk 1976	Wrong population
Von Mundy 1956	Wrong population
Walter 1979	Not a study
Warne 1987	Not a study
Wasielewski 2001	Wrong population
Watson 1987	Not a study
Watt 1980	Wrong intervention
Watt 1981	No relevant data
Wenting 1981	Wrong population
Whyte 2014	Wrong study design
Williams 1985	Wrong population

APPENDICES

Appendix 1. Cochrane Neuromuscular Specialised Register (CRS Web) search strategy

Search run on 11 November 2019

#1 orthostatic NEAR hypotens* AND INREGISTER

#2 orthostatic NEAR intolerance AND INREGISTER

#3 postural NEAR hypotens* AND INREGISTER

#4 neurally NEAR mediated NEAR hypotens* AND INREGISTER

#5 autonomic NEAR hypotens* AND INREGISTER

#6 #1 OR #2 OR #3 OR #4 OR #5 AND INREGISTER

#7 fludrocortisone* or florinef* or fluorocortisol* or fluorohydrocortisone* AND INREGISTER

#8 #6 AND #7 and INREGISTER

Appendix 2. Cochrane Register of Controlled Trials (CENTRAL in CRS Web Online) search strategy

Search run on 11 November 2019

#1 orthostatic NEAR hypotens* AND CENTRAL:TARGET

#2 orthostatic NEAR intolerance AND CENTRAL:TARGET

#3 postural NEAR hypotens* AND CENTRAL:TARGET

#4 neurally NEAR mediated NEAR hypotens* AND CENTRAL:TARGET

#5 autonomic NEAR hypotens* AND CENTRAL:TARGET

#6 #1 OR #2 OR #3 OR #4 OR #5 AND CENTRAL:TARGET

#7 fludrocortisone* or florinef* or fluorocortisol* or fluorohydrocortisone* AND CENTRAL:TARGET

#8 #6 AND #7 AND CENTRAL:TARGET

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to November 08, 2019>

Search Strategy:

---

1 Hypotension, Orthostatic/ (5558)

2 orthostatic hypotens*.mp. (5119)

3 postural hypotens*.mp. (1471)

4 orthostatic intolerance.mp. (1325)

5 neurally mediated hypotens*.mp. (53)

6 autonomic hypotens*.mp. (1)

7 or/1-6 (9928)

8 (fludrocortisone* or florinef*).mp. (2182)

9 (fluorocortisol* or fluorohydrocortisone*).mp. (262)

10 8 or 9 (2275)

11 7 and 10 (317)

12 exp animals/ not humans/ (4641527)

13 11 not 12 (317)

14 remove duplicates from 13 (317)

Appendix 4. Embase (OvidSP) search strategy

Database: Embase <1974 to 2019 November 08>

Search Strategy:

---

1 orthostatic hypotension/ (19939)

2 orthostatic hypotens*.tw. (7694)

3 postural hypotens*.mp. (1925)

4 orthostatic intolerance.mp. (2199)

5 neurally mediated hypotens*.mp. (73)

6 autonomic hypotens*.mp. (4)

7 or/1-6 (23568)

8 (fludrocortisone* or florinef*).mp. (6967)

9 (fluorocortisol* or fluorohydrocortisone*).mp. (170)

10 8 or 9 (7002)

11 7 and 10 (1325)

12 exp animal/ or exp invertebrate/ or animal.hw. or non human/ or nonhuman/ (26597824)

13 human/ or human cell/ or human tissue/ or normal human/ (20333794)

14 12 not 13 (6329961)

15 11 not 14 (1323)

16 limit 15 to (conference abstracts or embase) (1286)

Appendix 5. CINAHL (EBSCOhost) search strategy

Monday, November 11, 2019 11:20:59 AM

S9 S6 AND S7 Limiters - Exclude MEDLINE records

Search modes - Boolean/Phrase 13

S8 S6 AND S7 39

S7 fludrocortisone* or florinef* or fluorocortisol* or fluorohydrocortisone* 168

S6 S1 OR S2 OR S3 OR S4 OR S5 2,166

S5 "neurally mediated hypotens*" 11

S4 "orthostatic intolerance" 292

S3 "postural hypotens*" 233

S2 "orthostatic intolerance" 292

S1 orthostatic N3 hypotens* 1,825

Appendix 6. Additional search strategy

Searches

EMBASE.com

Date Searched: 9 August 2017

#1 'crossover procedure'/exp

#2 'double blind procedure'/exp

#3 'single blind procedure'/exp

#4 'randomized controlled trial'/exp

#5 random*:ti,ab OR crossover*:ti,ab OR ((cross NEXT/1 over*):ti,ab) OR placebo*:ti,ab OR ((doubl* NEAR/1 blind*):ti,ab) OR allocat*:ti,ab

#6 trial:ti

#7 'controlled clinical trial'/exp

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 'animal'/exp OR 'invertebrate'/exp OR animal:de OR 'nonhuman'/exp

#10 'human'/exp OR 'human cell'/exp OR 'human tissue'/exp OR 'normal human'/exp

#11 #9 NOT #10

#12 #8 NOT #11

#13 #12 AND [embase]/lim

#14 'orthostatic hypotension'/exp

#15 (orthostatic NEXT/1 hypotension):ti,ab

#16 postural NEXT/1 hypotension

#17 orthostatic NEXT/1 intolerance

#18 neurally NEXT/1 mediated NEXT/1 hypotension

#19

MEDLINE (OvidSP) search strategy

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Ovid MEDLINE(R) Daily Update 29 October 2017

Searches

1 Hypotension, Orthostatic/

2 orthostatic hypotens*.tw,kf.

3 postural hypotens*.tw,kf.

4 orthostatic intolerance.tw,kf.

5 neurally mediated hypotens*.tw,kf.

6 autonomic hypotens*.tw,kf.

7 or/1-6

8 (fludrocortisone* or florinef*).tw,kf.

9 (fluorocortisol* or fluorohydrocortisone*).tw,kf.

10 8 or 9

11 (exp animals/ not humans/) or (bovine or canine or capra or cat or cats or cattle or cow or cows or dog or dogs or equine or ewe or ewes or feline or goat or goats or horse or horses or invertebrate or invertebrates or macaque or macaques or mare or mares or mice or monkey or monkeys or mouse or ovine or pig or pigs or porcine or primate or primates or rabbit or rabbits or rat or rats or rattus or rhesus or sheep or simian or sow or sows or vertebrate or vertebrates).ti.

12 10 not 11

13 remove duplicates from 12

Cochrane Central Register of Controlled Trials (OvidSP EBM Reviews)

September 2017

Searches

1 orthostatic hypotens*.ti,ab,kw.

2 orthostatic intolerance.ti,ab,kw.

3 postural hypotens*.ti,ab,kw.

4 "neurally mediated hypotens*".ti,ab,kw.

5 autonomic hypotens*.ti,ab,kw.

6 or/1-5

7 (fludrocortisone* or florinef*).ti,ab,kw.

8 (fluorocortisol* or fluorohydrocortisone*).ti,ab,kw.

9 or/7-8

10 and/6-9

Appendix 7. Methods relating to meta-analysis included in the protocol

Data collection and analysis

Data extraction and management

One author will enter outcome data into RevMan and a second author will check data entry.

Measures of treatment effect

For dichotomous outcome measures, we will calculate the risk ratios (RR) and risk differences (RD) with 95% confidence intervals (CIs). For continuous measures, we will report the mean difference (MD) and 95% CI, or standardized mean difference (SMD) and 95% CI when different measurement scales are used for the same outcome. We will use the Cochrane statistical package, Review Manager 5 (RevMan 5; RevMan 2020) for data analysis.

Dealing with missing data

If data are unavailable, we will assess whether data are likely to be missing at random. If yes, we will only analyze the available data. If data are not missing at random, we will perform sensitivity analyses to assess how sensitive results are to imputations of the missing data, with all good outcomes, poor outcomes and the mean. We will then analyze the potential impact of missing data as part of the 'Risk of bias' assessment in included studies.

Assessment of heterogeneity

We will assess heterogeneity using the Chi^2 test and I^2 statistic (Higgins 2003). Where significant heterogeneity is present, we will attempt to determine potential reasons by examining population and study characteristics and perform subgroup analyses to explore their influence when possible (Deeks 2020).

Assessment of reporting biases

For quantitative analyses, we will inspect forest plots and prepare funnel plots to look for evidence of reporting bias. We will present funnel plots if 10 or more studies are identified (Page 2020).

Data synthesis

When available and sufficiently clinically homogeneous, we will combine data from included RCTs in meta-analyses. As we are anticipating some natural heterogeneity among the study populations, we have chosen a random-effects model for our statistical analyses. We will conduct analyses using RevMan 5 software (RevMan 2020) for all statistical analyses. We will use a narrative synthesis approach to review the literature for all non-randomized studies and for randomized studies that provide insufficient data to conduct a meta-analysis. Results from RCTs and non-randomized studies will be reported in the results section (Deeks 2020).

Subgroup analysis and investigation of heterogeneity

As data permits, we will carry out the following a priori subgroup analyses on all outcomes.

- Peripheral autonomic failure versus central autonomic failure
- Disease state (e.g. Parkinson Disease, diabetes, amyloid-induced orthostatic hypotension, pure autonomic failure, Lewy body disease, or multiple system atrophy)
- Age 65 years or over versus under 65 years

To detect differences between two subgroups, we will consider both the difference in the magnitude of effect as well as the overlap in confidence intervals. To detect differences between three or more subgroups, we will use the formal test for subgroup interactions in RevMan 5 (RevMan 2020).

Sensitivity analysis

As data permits, we will perform sensitivity analyses that are restricted to studies with unclear to low risk of bias, those conducted in the USA, UK or other high-income country, those with non-industry funding, or English-language studies, those with attrition rates greater than 20%, those with missing data, those more than 3 weeks long, and those that use validated measurements, to explore their influence on effect size.

Summary of findings and assessment of the certainty of the evidence

If sensitivity analyses indicate outcomes measured at less than three weeks are unreliable (an important source of heterogeneity), in the 'Summary of findings' table we will only report measurements taken at three weeks or longer. We will use the assumed risks as reported in included studies.

Appendix 8. Supporting information for prioritization of five out of 13 studies as best evidence

Study	Best evidence?	Rationale
Axelrod 2005	Yes	Observational study and met all applicable POST-I criteria. Addresses gap in evidence by examining the long-term effects (nearly 40 years) of fludrocortisone in people with familial dysautonomia.
Axelrod 1997	No	Observational study but did not report baseline differences between groups and didn't account for it in analysis (“No” to POST-I item #5)
Campbell 1975	Yes	RCT
Campbell 1976	No	Observational study but did not use repeated measures at baseline and follow-up (“No” to POST-I item #6) and could not rule out that effect was due to confounding (“No” to POST-I item #7)

(Continued)

Chobanian 1979	No	Observational study but was not particularly careful at measuring outcomes ("No" to POST-I item #6) and could not rule out that effect was due to confounding ("No" to POST-I item #7)
Kochar 1978	No	Observational study but was not particularly careful at measuring outcomes ("No" to POST-I item #6) and could not rule out that effect was due to confounding ("No" to POST-I item #7)
Matsubara 1990	No	Observational study but was not particularly careful at measuring outcomes ("No" to POST-I item #6) and could not rule out that effect was due to confounding ("No" to POST-I item #7)
Pathak 2005a	No	Observational study but did not report baseline differences between groups and didn't account for it in analysis ("No" to POST-I item #5)
Pathak 2005b	No	Observational study but did not report baseline differences between groups and didn't account for it in analysis ("No" to POST-I item #5)
Schatz 1976	No	Observational study but was not particularly careful at measuring outcomes ("No" to POST-I item #6) and could not rule out that effect was due to confounding ("No" to POST-I item #7)
Schoffer 2007	Yes	RCT
Schreglmann 2017	Yes	RCT
Ten Harkel 1992	Yes	Observational study and met all applicable POST-I criteria. Addresses gap in evidence by examining long-term (14 months) effects and harms of fludrocortisone in people with orthostatic hypotension from a variety of underlying conditions.

Appendix 9. Basic study characteristics of eight de-prioritized studies

Study	Study design	Sample size	Description of study
Axelrod 1997	Case-control	N = 18	Evaluates response to non-invasive tests among 10 people with family dysautonomia and 8 healthy controls while supine and at 90 degrees tilt. Goal was to determine if autonomic dysfunction involves cardiac as well as peripheral vascular integrity. The participants with family dysautonomia were tested before and 1 hour after receiving oral fludrocortisone or midodrine.
Campbell 1976	Case series	N = 13	Describes long-term follow-up (mean 12 months) of 13 people receiving fludrocortisone for diabetic postural hypotension.
Chobanian 1979	Case series	N = 7	Describes effects of fludrocortisone among 7 people with orthostatic hypotension in terms of hypotension while in recumbent and standing positions.
Kochar 1978	Case series	N = 5	Describes effects of indomethacin in 5 people compared to either propranolol or fludrocortisone.
Matsubara 1990	Case series	N = 9	Describes effects of fludrocortisone in 9 people with Shy-Drager syndrome when moving from supine to sitting up.

(Continued)

Pathak 2005a	Cohort	N = 121	Examines adverse drug reactions to drugs used in France for orthostatic hypotension, including fludrocortisone.
Pathak 2005a	Cohort	N = 31	Examines effects of heat on people with neurogenic orthostatic hypotension of varying etiologies, a subgroup of which received fludrocortisone.
Schatz 1976	Case series	N = 23	Describes response (satisfactory, excellent, good, fair, unsatisfactory) to fludrocortisone treatment among 23 people with orthostatic hypotension of varying etiologies (i.e. idiopathic, diabetes, Shy-Drager, undifferentiated CNS disease, previous gastric surgery, amyloidosis).

Appendix 10. Clinical trials registries search strategies

We searched the US National Institutes for Health Clinical Trials Registry, ClinicalTrials.gov (www.clinicaltrials.gov/), the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) and ISRCTN registry (www.isrctn.com) on 23 September 2019.

Database or Resource	Strategy	Results
Clinicaltrials.gov	[Advanced Search] Condition: (orthostatic OR postural) AND hypotension Other terms: fludrocortisone OR florinef OR fluorocortisol	6 studies
apps.who.int/trialsearch/	[Advanced Search] Condition: orthostatic hypotension OR postural hypotension AND Intervention: fludrocortisone OR florinef OR fluorocortisol Recruitment status: ALL	2 studies
www.isrctn.com	[Advanced Search] Intervention: fludrocortisone	3 studies

WHAT'S NEW

Date	Event	Description
24 May 2021	Amended	Corrections to sources of support and author affiliation

HISTORY

Protocol first published: Issue 12, 2017
Review first published: Issue 5, 2021

CONTRIBUTIONS OF AUTHORS

SRR and CHG conceived the review and drafted the initial protocol and the search strategy with assistance from the Cochrane team.

All review authors contributed to and revised the draft. All review authors have approved publication of the review.

Dr Mark Helfand will be the guarantor of the review.

DECLARATIONS OF INTEREST

MH: none known

YA: none known

KAC: none known

CHG: Dr Gibbons has served on an advisory board for Lundbeck on the treatment of orthostatic hypotension.

SRR: Dr Raj has served on the Board of Directors of multiple professional scientific organizations (American Autonomic Society and the Association of Clinical & Translational Sciences) and as a Medical Advisor for multiple Patient Advocacy Groups. He was not financially compensated for these activities. He has received grants from the National Institutes of Health (USA) and Canadian Institutes for Health Research for studies on Postural Tachycardia Syndrome and his colleague has received funding from the Canadian Institutes for Health Research for a study of fludrocortisone in vasovagal syncope. Dr Raj has also received study drug from Apotex Pharmaceuticals for a study of atomoxetine in vasovagal syncope. He has been compensated for and served as a consultant for Lundbeck Pharmaceuticals, GE Healthcare and Medtronic Inc. Dr Raj has been compensated for and served as an expert witness in a case involving whether a car accident caused Postural Tachycardia Syndrome in a patient.

KP: none known

SV: none known

SOURCES OF SUPPORT

Internal sources

- The authors completed this review within their own time, as there is no allocated time or funding for such activities within their jobs. This material is the result of work supported with resources and the use of facilities at VA Portland Medical Center, USA

  The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We developed and used a screening tool (Portland Observational Study Screening Tool for Interventions [POST-I]; Figure 1) to prioritize studies that offered the best available evidence to address our review question. We only conducted formal risk of bias and data extraction on prioritized studies. We described the process for data entry and checks.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Diabetes Mellitus; Domperidone [therapeutic use]; Dysautonomia, Familial [complications]; Fludrocortisone [*therapeutic use]; Hypotension, Orthostatic [*drug therapy]; Observational Studies as Topic; Parkinson Disease [complications]; Pyridostigmine Bromide [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans