Midodrine for orthostatic hypotension and recurrent reflex syncope

A systematic review

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ABSTRACT

Objective: Symptomatic orthostatic hypotension (SOH) and recurrent reflex syncope (RRS) can be disabling. Midodrine has been proposed in the management of patients with these conditions but its impact on patient important outcomes remains uncertain. We performed a systematic review to evaluate the efficacy and safety of midodrine in patients with SOH and RRS.

Methods: We searched multiple electronic databases without language restriction from their inception to June 2013. We included randomized controlled trials of patients with SOH or RRS that compared treatment with midodrine against a control and reported data on patient important outcomes. We graded the quality of evidence according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Results: Eleven trials involving 593 patients were included in this review. Three studies addressed health-related quality of life in patients with RRS, showing improvement with midodrine: risk difference 14% (95% confidence interval [CI] −3.5 to 31.6), very low confidence. Seven studies addressed symptom improvement and provided poolable data showing improvement with midodrine in patients with SOH: risk difference 32.8% (95% CI 13.5–48), low confidence; and RRS: risk difference 63.3% (95% CI 47.6–68.2), very low confidence. Five studies reported syncope recurrence in patients with RRS showing improvement with midodrine: risk difference 37% (95% CI 20.8%–47.4%), moderate confidence. The most frequent side effects in the midodrine arm were pilomotor reactions (33.6%, risk ratio 4.58 [95% CI 2.03–10.37]).

Conclusions: Evidence warranting low/moderate confidence suggests that midodrine improves clinical important outcomes in patients with SOH and RRS. *Neurology*® 2014;83:1170–1177

GLOSSARY

CI = confidence interval; **FDA** = Food and Drug Administration; **GRADE** = Grading of Recommendations Assessment, Development and Evaluation; **HRQL** = health-related quality of life; **NNT** = number needed to treat; **OH** = orthostatic hypotension; **RCT** = randomized controlled trial; **RD** = risk difference; **RR** = risk ratio; **RRS** = recurrent reflex syncope; **SF-36** = 36-Item Short Form Health Survey; **SH** = supine hypertension; **SOH** = symptomatic orthostatic hypotension.

Symptomatic orthostatic hypotension (SOH) and recurrent reflex syncope (RRS) (also known as neurally mediated syncope) are 2 conditions that cause significant morbidity.[1,2] Although they differ substantially from a pathophysiologic point of view,[3] the absence of an adequate vasoconstrictive response has a central role in both.[4,5] Furthermore, these conditions overlap in a significant proportion of patients presenting to the emergency department for transient loss of consciousness.[6] Midodrine hydrochloride, an α_1-adrenergic receptor agonist, is currently recommended for the treatment of both SOH and RRS in most of the clinical practice guidelines.[7,8]

Nevertheless, the lack of high-quality evidence supporting the utilization of this drug recently raised concerns, and the Food and Drug Administration (FDA), which approved the drug under the FDA's accelerated-approval process based on surrogate endpoints, threatened to withdraw midodrine from the market. After patients taking the medication and their prescribing physicians expressed concerns about midodrine removal, the FDA backed down. The agency reached

Supplemental data at Neurology.org

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an agreement with Shire to have the company conduct trials that may satisfy the agency efficacy standard.[9]

Although an optimal assessment of the evidence addressing midodrine potential benefits requires evaluation of its effects on symptoms and adverse effects, most of the trials have focused on surrogate outcomes such as changes in blood pressure, heart rate, or laboratory studies (tilt test). Four recently published systematic reviews evaluating midodrine for the treatment of SOH or vasovagal syncope[10–13] failed to adequately assess all the existing evidence (table e-1 on the *Neurology*® Web site at Neurology.org).

We therefore conducted a systematic review and meta-analysis to evaluate the efficacy and safety of midodrine in patients with orthostatic hypotension (OH) secondary to autonomic dysfunction and RRS.

METHODS

Data sources and searches. We searched for relevant articles without language restriction in the following electronic databases: MEDLINE, EMBASE, CINAHL, LILACS, Cochrane Central Register of Controlled Trials, from database inception to June 2013. The search terms for PubMed were as follows: "midodrine" [MeSH] OR Midodrin OR Midodrina OR "midodrine HCL" OR midodrinum OR midodrine hydrochloride OR Proamatine OR Gutron.

In addition, we searched Google Scholar,[14] clinicaltrials.gov, and screened references of included studies and reviews. We also contacted the drug manufacturer (Shire Development LLC.) and occasionally made inquiries regarding other published or unpublished studies known to the authors of the primary studies (see results section).

Study selection. Two reviewers (A.I. and C.G.M.) addressed eligibility and data abstraction. We used κ statistic to assess agreement between reviewers.

Study design. We included randomized controlled parallel group trials and randomized crossover trials that compared treatment with midodrine against a control (placebo, no treatment, or supportive treatment), enrolled patients of any age with a diagnosis of RRS or SOH as defined in appendix e-1 or similar, and tested oral midodrine (daily doses from 2.5 to 30 mg) alone or associated with standard care (reassurance regarding the benign nature of the condition, maintaining an adequate fluid and salt intake, regular exercise, and the application of physical counterpressure maneuvers) or other drugs.

Outcome measures. We included only studies that evaluated at least one of the following patient-important outcomes in both midodrine and comparator arms:

- Health-related quality of life (HRQL) assessed by any validated questionnaire
- Symptom improvement defined as any improvement reported by the patient in symptoms attributed to OH or recurrent syncope
- Syncope recurrence
- Drug-related adverse effects: goose bumps, tingling, chills, or any other pilomotor reactions, agitation, depression, anxiety, insomnia, gastrointestinal discomfort, palpitations, and urinary problems (urinary retention, hesitancy, or urgency)

Data extraction and quality assessment. The 2 reviewers independently and in duplicate extracted trial details pertaining to the participants, interventions, comparators, and results, and assessed the confidence in estimates of effect.

Confidence in estimate assessment. As suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group,[15] we considered issues of risk of bias,[16] precision,[17] consistency,[18] directness,[19] and publication bias[20] in making an overall rating of confidence in effect estimates (quality of evidence) for each outcome. Details are described in appendix e-2.

Handling of discrepancies. We resolved discrepancies in eligibility, data abstraction, risk of bias, and GRADE confidence in estimate assessment by discussion.

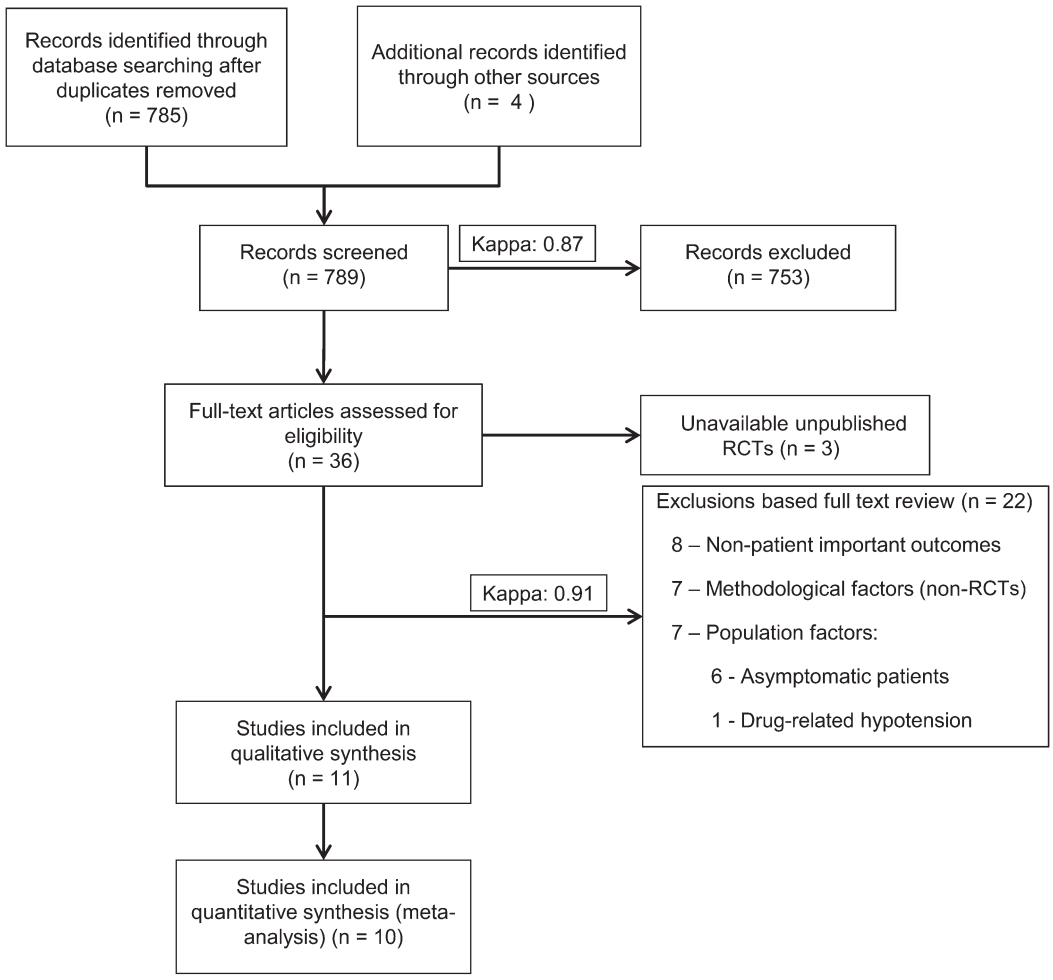
Data synthesis and analysis. All pooled estimates used random-effects models provided by Review Manager (RevMan) (version 5.2; The Nordic Cochrane Centre, The Cochrane Collaboration, 2012, Copenhagen). The statistical method used was inverse variance for continuous data and combined continuous/dichotomous data, and Mantel–Haenszel for dichotomous data. For calculating risk differences (RDs), we applied relative effects to the median control group risk estimate from the included studies when possible. For crossover trial data, we adopted a conservative approach and assumed that there was no correlation between observations on the same patient. Details pertaining to HRQL and symptom improvement outcome analysis are described in appendix e-3.

Heterogeneity. To quantify the inconsistency among the pooled estimates, we used the χ^2 test and I^2 statistic. We conducted subgroup analysis based on the following a priori hypotheses when 5 or more trials were pooled: (1) risk of bias: we anticipated smaller effects in publications with low or moderate risk of bias; (2) length of follow-up: we anticipated smaller effects and fewer adverse effects with shorter follow-up using a threshold of $\leq$3 months vs $>$3 months; (3) midodrine dose: we anticipated larger effects and more adverse effects with higher doses (after looking at the study's results, we decided to use a threshold of $<$15 vs $>$15 mg/d); and (4) patient age: we considered possible different treatment response and adverse-effect profile between pediatric and adult patients. We also conducted post hoc subgroup analysis based on the following hypothesis: (1) midodrine dose adjustment: we hypothesized larger effects in trials in which midodrine dose was adjusted based on patient clinical response; and (2) cointerventions: we hypothesized larger effects in trials that allowed pharmacologic and nonpharmacologic cointerventions. For each subgroup analysis, we tested for interaction by using a χ^2 significance test. We also performed a sensitivity analysis excluding trials with (1) crossover design, and (2) high risk of bias.

RESULTS

After excluding the duplicate and irrelevant publications by title, we identified and assessed for inclusion 36 references (32 published and 4 unpublished). Of these, we excluded 25 (figure 1), leaving 11 trials[21–31] (593 patients) for data extraction (table 1, full version in table e-2). Of the 4 unpublished studies, we identified 3 in clinicaltrials.org[28,32,33] (2 "completed" status and 1 "terminated status") and one that was mentioned in another publication[34] (see publication bias). Kappa for eligibility assessment was high or very high throughout the selection process. We

Figure 1 Trial selection flow diagram



RCT = randomized controlled trial.

contacted one of the authors of one of the included randomized controlled trials (RCTs)[24] and one author of a study that mentioned another unpublished RCT,[34] who replied that they could not provide additional information. We tried unsuccessfully to contact the authors of 3 of the included RCTs.[25,27,31] Table e-3 presents the risk of bias assessment for each outcome.

Publication bias. All of the included studies were relatively small, and at least half of them have industry sponsorship (table 1, full version in table e-2). We identified one completed and one terminated registered unpublished RCT[32,33] whose results were not available. We contacted the sponsor (Shire Development LLC), who refused to provide any unpublished information. We identified a publication in which an OH symptom assessment scale was developed based on an unpublished RCT,[34] but we could not gain access to its results. Overall, the 2 finished unavailable trials included 224 patients. Only one unpublished RCT could be included in our review and reported no statistically significant improvement in symptoms related to OH. Based on this, we assume high risk of publication bias.

Health-related quality of life. ***Patients with SOH.*** No studies evaluated this outcome.

Patients with RRS. Three studies evaluated this outcome. Two have moderate risk of bias and used the 36-Item Short Form Health Survey (SF-36),[25,31] and one has high risk of bias and used the Endicott instrument[27] (table e-3).

Because only 1 of the 3 eligible trials reported the change in HRQL, we used postintervention results to calculate weighted difference of means. We converted the results of the trial that used the Endicott scale[27] (range of possible results 14–70) to the SF-36 instrument scores (range of possible results 0–100). The results showed HRQL difference in favor of midodrine (mean difference 13.69, 95% confidence interval [CI] 0.09–27.2, I^2 77%) (figure 2A). Considering a minimally important difference of 5 points[35] and a mean pooled SF-36 score in control arms of 39.6, we set the significant HRQL

Table 1 Design and baseline characteristics of included trials

Study design (year)	Type of participants	Intervention/comparison	Follow-up	Supported by
RCT crossover (1974)[21]	87 adults with symptomatic orthostatic hypotension (pathologies not described)	Midodrine 2.5 or 5 mg tid/placebo	20 d	ND
RCT parallel (1993)[22]	97 adult patients with symptomatic orthostatic hypotension and a history of syncope or near syncope (Bradbury-Eggleston syndrome [20%], Shy-Drager syndrome [18%], diabetes [27%], Parkinson disease [22%], other [10%])	Midodrine, 2.5 mg, 5 mg, or 10 mg tid/placebo	4 wk	Roberts Pharmaceutical Corp.
RCT crossover (1995)[23]	8 adult patients with symptomatic orthostatic hypotension (Bradbury-Eggleston syndrome [87%], Shy-Drager syndrome [13%])	Midodrine 2.5, 5, 7.5, 10 mg tid; epinephrine 6, 12, 18, 24 mg/placebo	10 d	Roberts Pharmaceutical Corp.
RCT parallel (1997)[24]	171 adult patients with symptomatic orthostatic hypotension (Bradbury-Eggleston syndrome [23%], Shy-Drager syndrome [25%], diabetes [23%], Parkinson disease [12%], other [18%])	Midodrine 10 mg tid/placebo	6 wk	Roberts Pharmaceutical Corp.
RCT crossover (1998)[25]	16 adult patients with history of frequent neurocardiogenic syncope	Midodrine 5 mg tid/placebo	2 mo	ND
RCT crossover (1998)[26]	27 adult patients with symptomatic orthostatic hypotension (Bradbury-Eggleston syndrome [51%], Shy-Drager syndrome [25%], diabetes [11%], Parkinson disease [4%], other [9%])	Midodrine 2.5, 10, and 20 mg qd/placebo	6 d	Roberts Pharmaceutical Corp.
RCT parallel (2001)[27]	61 adult patients with a history of recurrent neurocardiogenic syncope with positive head-up tilt test	Midodrine 5–15 mg tid/fluid therapy, salt tablets, and counseling	6 mo	ND
RCT crossover (2005)[28]	24 adult ambulatory patients with symptomatic orthostatic hypotension	Midodrine 10–30 mg qd/placebo	30 d	Shire, Inc.
RCT (2006)[29]	26 pediatric patients with recurrent vasovagal syncope and positive head-up tilt test	Midodrine 1.25–2.5 mg bid/placebo	10 mo	National Tenth Five Year Plan Research Project of China and the Major Basic Research Project of China
RCT (2009)[30]	48 pediatric patients with recurrent vasovagal syncope and positive head-up tilt test	Midodrine 1.25–2.5 mg bid/fluid therapy, salt tablets, and counseling	9 mo	ND
RCT crossover (2011)[31]	28 adult patients with recurrent vasovagal syncope	Midodrine 5 mg bid/placebo	3 mo	NIH and National Aeronautics and Space Administration

Abbreviations: bid = 2 times a day; ND = not described; qd = once a day; RCT = randomized controlled trial; tid = 3 times a day.

improvement threshold at 45.[36] The calculated control HRQL improvement rate was 45% and the difference in the proportion of patients with significant HRQL improvement with midodrine was 14% (95% CI -3.5% to 31.6%; number needed to treat [NNT] 7 [95% CI number needed to harm 28 to NNT 3]) (table 2). Sensitivity analysis showed that results could significantly change if missing data were included. Other sensitivity analyses showed no important differences.

Confidence in estimates. The confidence in estimates was very low (table e-4) because of moderate to high risk of bias (table e-3), imprecision, and publication bias.

Symptom improvement. ***Patients with SOH.*** Six studies evaluated this outcome. Five have moderate risk of bias[22–24,26,28] and one has high risk of bias[21] (table e-3). We decided to pool all the included trials except one.[23] That study reported a significant increase in the ability to stand in 8 patients treated with midodrine compared with placebo ($p < 0.001$), but did not used any symptom improvement scale.

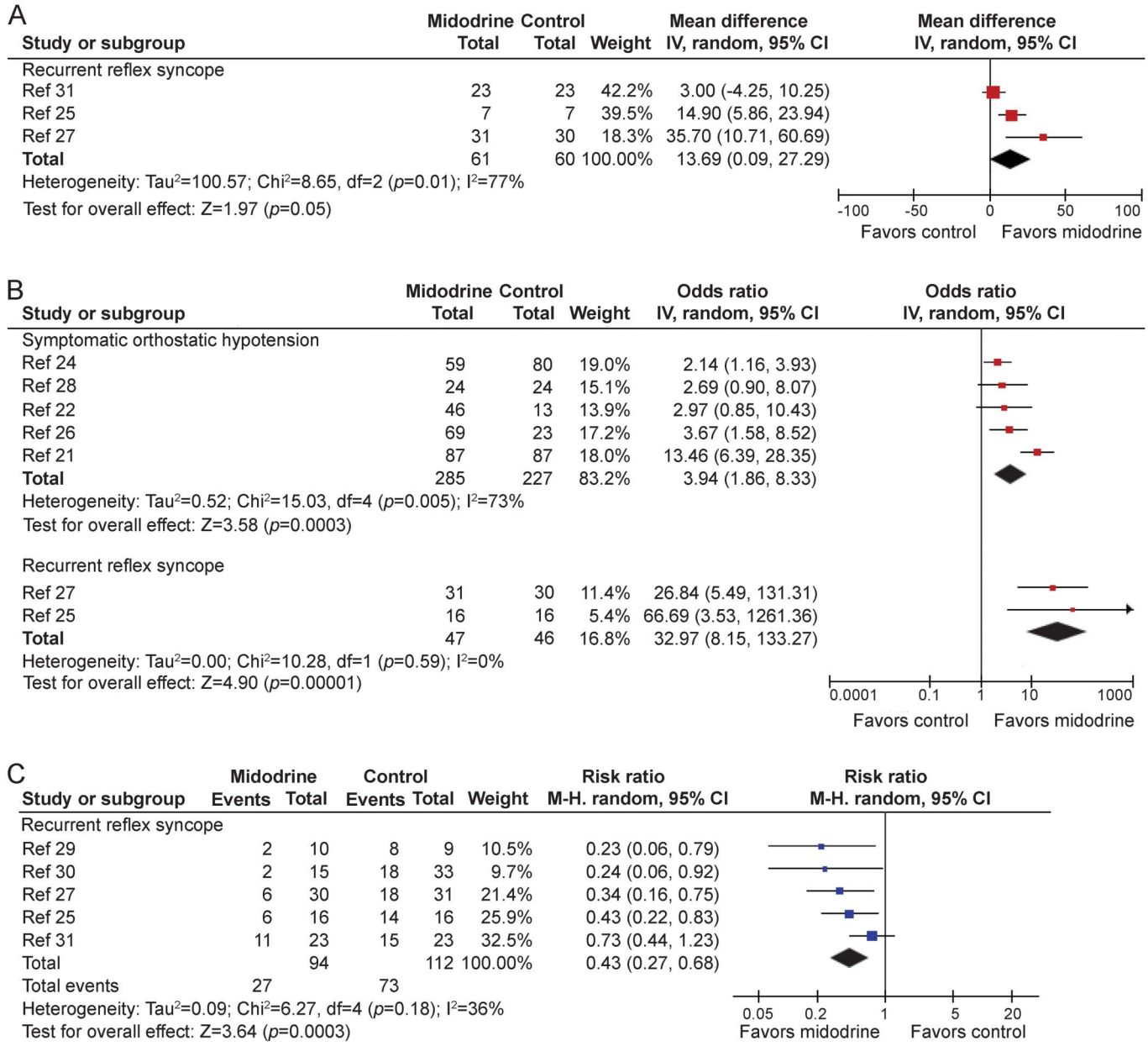
Estimated symptom improvement in the control arm was 30%. The results showed symptom improvement in the midodrine arm: odds ratio 3.9 (95% CI 1.8–8.3), RD 32.8% (95% CI 13.5%–48%), NNT 3 (95% CI 2–7), I^2 73% (figure 2B, table 2). Sensitivity analysis showed that results could significantly change only if missing data were included applying the most stringent assumption (strategy 3, appendix e-2). Subgroup analysis showed, as predicted, smaller effect in the low/moderate risk of bias subgroup ($p < 0.05$), but the results remained robust after excluding high risk of bias trial results in a sensitivity analysis. Other subgroup and sensitivity analyses showed no important differences.

Confidence in estimates. The confidence in estimates was low (table e-4) because of moderate risk of bias (table e-3), imprecision, indirectness, and publication bias.

Patients with RRS. Two studies evaluated this outcome. One has moderate risk of bias[25] and one high risk of bias[27] (table e-3).

Estimated symptom improvement in the control arm was 30%. The results showed symptom improvement in the midodrine arm: odds ratio 32.9 (95% CI 8.1–133.2), RD 63.3% (95% CI 47.6%–68.2%), NNT 2 (95% CI 1–2), I^2 0% (figure 2B, table 2). Sensitivity analyses showed no important differences.

Figure 2 Forest plots of midodrine effectiveness



(A) Mean difference in health-related quality of life SF-36 scale (range 0–100) between midodrine and control. (B) Comparison of the proportion of patients with significant symptom improvement between midodrine and control. (C) Risk of syncope recurrence in midodrine vs control. CI = confidence interval; IV = inverse variance method; M-H = Mantel-Haenszel method; Ref = reference; SF-36 = 36-Item Short Form Health Survey.

Confidence in estimates. The confidence in estimates was very low (table e-4) because of high risk of bias (table e-3), imprecision, and publication bias.

Syncope recurrence. ***Patients with SOH.*** No studies evaluated this outcome.

Patients with RRS. Five studies evaluated this outcome: 2 have low risk of bias[25,31] and 3 have high risk of bias[27,29,30] (table e-3).

Median in the control arm was 65%. The results showed a reduction in syncope recurrence: risk ratio (RR) 0.43 (95% CI 0.27–0.68), RD 37% (95% CI 20.8–47.4), NNT 3 (95% CI 2–5), I^2 36% (figure 2C, table 2). Sensitivity analysis showed that results were robust to the most stringent assumptions regarding missing data. Subgroup analysis did not show significant differences. Other sensitivity analyses showed no important differences.

Confidence in estimates. The confidence in estimates was moderate (table e-4) because of imprecision and publication bias.

Adverse effects. We decided to pool side effects from trials including patients with RRS and SOH because we assumed the adverse-effect profile would be similar across those populations.

Table 2 Midodrine for symptomatic orthostatic hypotension and recurrent reflex syncope: Summary of findings

Types of participants, no. of studies/participants	Estimate of the effect	Assumed risk: Control group	Corresponding risk: Midodrine group	Quality of the evidence[a]
HRQL improvement (critical importance)				
RRS, 3/121[25,27,31]	MD (SF-36) 13.69 (95% CI 0.09–27.2)	450 patients per 1,000 will significantly improve HRQL despite not receiving midodrine[b]	140 more patients per 1,000 will significantly improve HRQL with midodrine (from 35 less to 316 more)[b]	Very low
OH	No studies evaluated this outcome			
Symptom improvement (critical importance)				
RRS, 2/93[25,27]	OR 32.9 (95% CI 8.1–133.2)	300 patients per 1,000 will significantly improve OH symptoms despite not receiving midodrine[c]	633 more patients per 1,000 will significantly improve symptoms with midodrine (from 476 to 682 more)[d]	Very low
OH, 5/512[21,22,24,26,28]	OR 3.9 (95% CI 1.8–8.3)	300 patients per 1,000 will significantly improve OH symptoms despite not receiving midodrine[c]	328 more patients per 1,000 will significantly improve symptoms with midodrine (from 135 to 480 more)[d]	Low
Syncope recurrence (critical importance)				
RRS, 5/206[25,27,29–31]	RR 0.43 (95% CI 0.27–0.68)	650 patients per 1,000 will have syncope recurrence if not receiving midodrine[c]	370 fewer patients per 1,000 will have syncope recurrence with midodrine (from 208 to 474 fewer)[d]	Moderate
OH	No studies evaluated this outcome			
Minor side effects (important)				
RRS/OH, 4/326[22,24,25,31]	RR 4.58 (95% CI 2.03–10.37)	36 patients per 1,000 will have symptoms despite not receiving midodrine[c]	128 more patients per 1,000 will have symptoms with midodrine (from 37 more to 337 more)[d]	Low
Urinary problems (critical importance)				
RRS/OH, 1/171[24]	None of the patients in the placebo arm had urinary problems vs 5 patients (6%) in the midodrine arm			Very low

Abbreviations: CI = confidence interval; HRQL = health-related quality of life; MD = mean difference; OH = orthostatic hypotension; OR = odds ratio; RR = risk ratio; RRS = recurrent reflex syncope; SF-36 = 36-Item Short Form Health Survey.

[a] Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence are as follows: "high quality indicates that further research is very unlikely to change our confidence in the estimate of effect; moderate quality indicates that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality indicates that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality indicates that we are very uncertain about the estimate."[15] For details, see table e-4.

[b] Calculated with the pooled mean (SD) control arm SF-36 score and the HRQL improvement threshold based on the minimally important difference.[35,36]

[c] Based on the median control group risk from all included trials who inform results as dichotomous.

[d] Based on the assumed risk in the comparison group and the relative effect of the intervention (95% CI).

Seven of the included studies reported adverse effects.[22–25,28,29,31] The most frequent side effects associated with midodrine were pilomotor reactions (pruritus/tingling of the scalp, goose bumps, "prickly feeling," paresthesiae, or piloerection), chills, and gastrointestinal discomfort, all of which were considered as "minor side effects." The results of those trials that reported the outcome in both midodrine and control arms[22,24,25,31] show an increase in the risk of minor side effects in midodrine-treated patients: RR 4.58 (95% CI 2.03–10.37), RD 12.8% (95% CI 3.7–33.7%), number needed to harm 8 (95% CI 3–27), I^2–14% (table 2).

The most frequent side effects that led to a discontinuation of midodrine were supine hypertension (SH), pilomotor reactions, and urinary problems (urinary retention, hesitancy, or urgency).

There was a nonstatistically significant increase in the risk of urinary problems in the only trial that reported this side effect in midodrine and placebo arms.[24]

Although we consider SH as a non–patient important outcome, we decided to report it because it was one of the main reasons for discontinuing the drug and it could be associated with an increase in the risk of stroke.[37,38]

Three studies reported SH in midodrine and placebo groups,[22–24] and showed an increase in the risk of SH in midodrine-treated patients: RR 5.31 (95% CI 1.39–20.27), RD 7% (95% CI 2%–11%), number needed to harm 14 (95% CI 9–50).

Confidence in estimates. The confidence in estimates was very low/low (table e-4) because of imprecision, indirectness, publication bias, and selective outcome reporting.

DISCUSSION In this systematic review, we identified 11 RCTs that evaluated the efficacy of midodrine in patients with SOH or RRS. The results showed that in both scenarios, midodrine might have a positive impact on clinical important outcomes and is not related to serious and life-threatening adverse effects. Nevertheless, it could be associated with some uncomfortable side effects, such as urinary urgency or retention, and pilomotor reactions, and SH whose clinical significance remains uncertain.[37,38] Overall, the quality of the evidence supporting the results is low/moderate, which means that our confidence in the effect estimate is limited and the true effect may be substantially different.[15] Furthermore, midodrine effectiveness could differ across subgroups of patients or could change according to the way the drug is administered. We explored those possibilities in subgroup and sensitivity analyses and found no differences related to patient age, midodrine dose, midodrine adjustment related to clinical response, or cointerventions.

It is also possible that the underlying pathology causing SOH could influence the clinical response rate. Among the included trials, Bradbury-Eggleston syndrome, Shy-Drager syndrome, diabetes, and Parkinson disease were the most prevalent diseases. Only one of the trials[24] formally examined this and another hypothesis (fludrocortisone or nonpharmacologic measures coadministration, severity of OH) in a subgroup analysis and found no significant differences. These results should be interpreted with caution considering the already mentioned low/moderate quality of evidence and the scarcity of trials evaluating different alternatives (i.e., midodrine dose in response to treatment was adjusted in only one of the included trials[23]). Because they are inexpensive and free of significant adverse reactions, nonpharmacologic measures (reassurance regarding the benign nature of the condition, maintaining an adequate fluid and salt intake, regular exercise, and the application of physical counter-pressure maneuvers) are recommended as the first step in the treatment of patients with RRS[8] and SOH.[7] These measures improve symptoms in a significant proportion of patients with the RRS,[39] but are less effective in patients with SOH.[40] Pharmacologic treatments such as midodrine should be considered in those who remain symptomatic after these measures are adequately instituted.

Consistent with our findings, most of the other published systematic reviews that evaluated midodrine in patients with SOH or RRS have informed benefits in HRQL,[10] improvement in SOH-related symptoms,[13] reduction in syncope recurrence,[10,11,13] and absence of serious adverse effects.[10,13] Only one of them informed absence of benefits on syncope recurrence or symptom improvement.[12] The overall quality of evidence in these reviews was judged as very low,[12] low,[13] or was not evaluated by any grading system (i.e., GRADE).[10,11]

The strengths of our systematic review include the following: (1) exhaustive search of published and unpublished trials—as a result of this search, we were able to include published and unpublished RCTs not identified in previous systematic reviews[21,28,30,31]; (2) focus on patient important outcomes evaluation; (3) multiple result analysis approaches as suggested by the GRADE Working Group[36]; and (4) transparent evaluation of the quality of evidence.

The main weakness of our systematic review is that we were not able to retrieve all of the existing published and unpublished information.

Low/moderate quality of evidence exists, suggesting that midodrine could significantly benefit patients with SOH and RRS. Health care providers, guideline developers, and policy-makers aiming to make decisions regarding the treatment of these patients should consider midodrine as one of the treatment alternatives, but must be aware of the uncertainty that exists related to the response rate among different subgroups of patients, and its long-term efficacy and safety.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design, data analysis, and data interpretation. A.I. and C.G.M. collected data and drafted the report, tables, and figures. All authors critically revised the manuscript and agreed on the final version.

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