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Effects of Atomoxetine for the Treatment of Neurogenic Orthostatic Hypotension in Patients With Alpha-synucleinopathies: A Systematic Review of Randomized Controlled Trials and a Focus-Group Discussion

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Background and Purpose Neurogenic orthostatic hypotension (nOH) is one of the most important nonmotor symptoms in patients with α-synucleinopathies. Atomoxetine is a selective norepinephrine transporter blocker that is a treatment option for nOH. This systematic review and expert focus-group study was designed to obtain evidence from published data and clinical experiences of Korean movement-disorder specialists about the efficacy and safety of atomoxetine for the pharmacological treatment of nOH in patients with α-synucleinopathies.

Methods The study comprised a systematic review and a focus-group discussion with clinicians. For the systematic review, multiple comprehensive databases including MEDLINE, Embase, Cochrane Library, CINAHL, PsycInfo, and KoreaMed were searched to retrieve articles that assessed the outcomes of atomoxetine therapy. A focus-group discussion was additionally performed to solicit opinions from experts with experience in managing nOH.

Results The literature review process yielded only four randomized controlled trials on atomoxetine matching the inclusion criteria. Atomoxetine effectively increased systolic blood pressure and improved OH-related symptoms as monotherapy or in combination with other drugs. Its effects were pronounced in cases with central autonomic failure, including multiple-system atrophy (MSA). Atomoxetine might be a safe monotherapy regarding the risk of supine hypertension.

Conclusions Atomoxetine is an effective and safe option for short-term nOH management, which could be more evident in patients with central autonomic dysfunction such as MSA. However, there is a paucity of evidence in the literature, and data from the focus-group discussion were inadequate, and so further investigation is warranted.

Keywords atomoxetine; orthostatic hypotension; systematic review; focus group.

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INTRODUCTION

According to the American Autonomic Society and American Academy of Neurology, orthostatic hypotension (OH) is defined as a decrease in systolic blood pressure (SBP) of at least 20 mm Hg or in diastolic blood pressure (BP) of at least 10 mm Hg within 3 minutes of standing or a head-up tilt of least 60° on a tilt table.[1] Neurogenic OH (nOH) results from a failure of sympathetic vasoconstriction and compensatory autonomic response, which occurs when in an upright body position.[2] It is one of the most important nonmotor symptoms and significantly affects the quality of life in patients with α-synucleinopathies, including

Parkinson's disease (PD), dementia with Lewy bodies (DLB), pure autonomic failure (PAF), and multiple system atrophy (MSA).[3] Several pharmacological treatments are currently available that reduce the symptoms related to nOH.[4] Fludrocortisone is a synthetic adrenal corticosteroid that increases sodium reabsorption and expands the plasma volume, while midodrine is a direct vasoconstrictor.[5] Droxidopa is a synthetic amino acid precursor that induces peripheral arterial and venous vasoconstriction.[5] However, the use of these agents is often restricted by adverse events, including supine hypertension and nonresponsiveness.[5]

Atomoxetine, a selective norepinephrine transporter blocker, has been approved by the US Food and Drug Administration (FDA) for treating attention deficit hyperactivity disorder (ADHD).[5] Its long-term efficacy and safety in patients with ADHD are well established.[6] Several previous studies have found that a daily atomoxetine dose of 18 mg was effective in relieving orthostatic BP decrease and OH-related symptoms in patients with nOH.[7-10] It has been used off label to manage nOH because it increases the availability of norepinephrine in the synaptic cleft.[5] However, the evidence for the efficacy of atomoxetine in nOH has not been comprehensively evaluated in a systematic review. A recent systematic review evaluated the effect of norepinephrine transport inhibition on the prevention of vasovagal syncope (VVS);[11] however, nOH has been found to have different mechanisms and hemodynamic patterns during tilt-table tests.[12] In VVS, the vasodepressor effect is associated with bradycardia and is triggered by centrally mediated inhibition of sympathetic influences.[12] Patients with VVS often maintain a steady BP for more than 10 minutes after head-up tilt, whereas patients with nOH cannot maintain their BP, which starts to decrease within 2–3 minutes of tilting.[12]

The purpose of this systematic review was to determine the efficacy and safety of atomoxetine in nOH. Following a systematic review, we carried out an expert focus-group study with Korean movement-disorder specialists to obtain their opinions and clinical concerns about atomoxetine as a pharmacological treatment option for nOH in patients with α-synucleinopathies.

METHODS

Systematic literature review

This study followed the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[13] (Supplementary Material 1 in the online-only Data Supplement), and the study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020191997).[14]

Data sources and search strategy

Multiple comprehensive databases including MEDLINE, Embase, Cochrane Library, CINAHL, PsycInfo, and KoreaMed were searched for studies that evaluated the outcomes of atomoxetine therapy in patients diagnosed with nOH published up to September 2, 2020. Further screenings of ClinicalTrials.gov and conference proceedings were conducted to identify relevant literature. The search terms for each database are displayed in Supplementary Material 2 (in the online-only Data Supplement).

Article selection and data extraction

All identified articles were managed using standard referencing management software (EndNote version X9, Clarivate Analytics, Philadelphia, PA, USA). After removing duplicates, two reviewers (Y.J.J. and A.K.) independently screened and reviewed the remaining articles. Any disagreements between the reviewers were referred to a third reviewer (W.H.H.) to achieve a consensus. A standardized data extraction method adapted from the Cochrane Collaboration model was applied by two independent reviewers (Y.J.J. and A.K.). The extracted data contained information about sample sizes, study methods, interventions, and outcomes. To obtain additional data not contained in the articles that were finally included in the systematic review, we requested the raw data from the original authors by sending several emails and consulting them using video conferencing.

Eligibility criteria

Types of studies

All types of articles that matched our criteria for participants, interventions, controls, and outcomes were searched for, with case reports, reviews, and editorials subsequently being excluded.

Types of participants

The included participants were adults older than 18 years and had a diagnosis of primary nOH. nOH is widely categorized into primary and secondary types.[15] Primary nOH is associated with underlying neurological disorders involving the autonomic nervous system, including PD, MSA, DLB, and PAF.[15] Secondary nOH is associated with spinal cord disorders and peripheral neuropathies such as amyloidosis and diabetes mellitus.[15] To exclude patients with secondary nOH, we obtained individual line-level data from the authors of the relevant studies, including all causes of nOH, and excluded any data related to secondary nOH. Bedridden patients and those with contraindications to atomoxetine (e.g., coronary artery disease, abnormal liver function, and narrow-angle glauco-

ma) were also excluded.

Types of intervention and control

This review compared the use of a daily atomoxetine dose of 18 mg with placebo.

Types of outcome measures

The primary outcome measure was a change in SBP in a sitting or standing position after the intervention. The secondary outcome measures were at least one measurement of symptoms associated with nOH and adverse events.

Quality assessment

The quality of included studies was evaluated using the Risk of Bias 2 (RoB2) tool for quality assessment developed by the Cochrane Collaboration.[16] The tool used was the RoB tool in RevMan (version 5.4.1). Six potential domains of bias were evaluated: selection, detection, performance, reporting, attrition, and other biases.

Focus-group discussion with experts

After the systematic review was complete, a group of Korean experts that specialized in movement disorders and frequently dealt with nOH in α-synucleinopathies was recruited for a semistructured survey to collate real-world data and clinical opinions. The authors aimed to include at least ten participants to ensure that all relevant opinions would be included.[17] Participants were informed about the purpose of the focus-group discussion and were encouraged to reflect on their clinical experiences. The survey consisted of five open-ended questions (Supplementary Material 3 in the online-only Data Supplement). An inductive thematic analysis was applied separately to data from the focus group of Korean movement-disorder specialists.[18] Emerging opinions were identified and classified into broader statements, which were more clearly described when considering the literature review findings.

RESULTS

Systematic literature review

Study search and selection

The process of identification, screening, and selection of included articles is illustrated in the PRISMA flow diagram in Fig. 1. Of 321 articles, 267 remained after duplicates were eliminated. Following title and abstract screening, only six articles were eligible for full-text screening. Four articles were finally included in the systematic review.

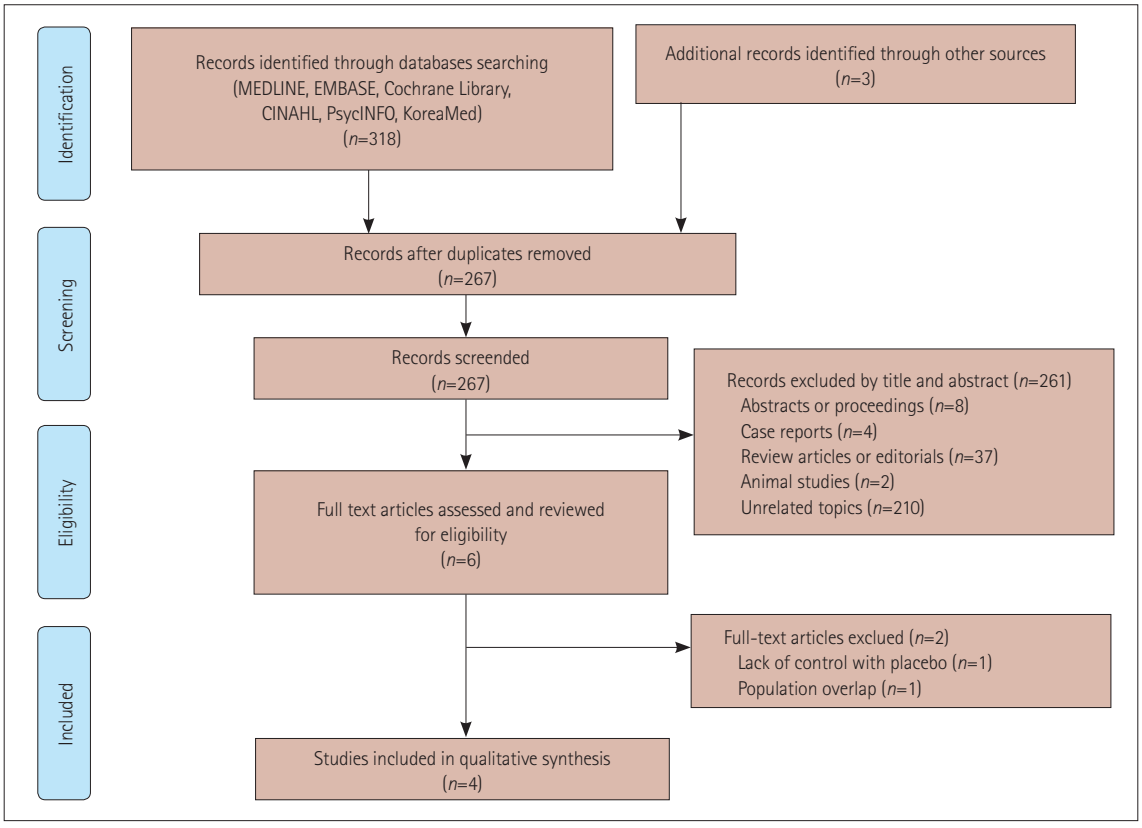

Fig. 1. Flowchart of the literature review process.

Participants and study characteristics

The characteristics of the four included studies[7-10] are listed in Table 1, all of which were randomized, placebo-controlled, single-blind, crossover studies. Since we planned to review the effect of atomoxetine on patients with primary nOH, we excluded a patient with amyloidosis from the study of Okamoto et al.[9] We also attempted to exclude patients with an undetermined cause of nOH from the studies of Okamoto et al.[9] and Ramirez et al.,[8] but this was not successful. Finally, 118 patients with primary nOH from 4 randomized controlled trials (RCTs) were included in this systematic review.

Effects of atomoxetine on BP

All four RCTs measured the seated and/or standing SBP at baseline and 60 minutes after drug administration (Table 2). Ramirez et al.[8] found that atomoxetine increased the seated

Table 1. Characteristics of the participants

Authors (year)	Study type	Sample size (no. of men)	Age (yr)†	Body weight (kg)†	BMI (kg/m²)†	Type of participants (*n*)
Okamoto et al.[9] (2019)	Single-blind crossover RCT	11* (6)	69±3	75±14	N/A	PAF (5), PD (2), MSA (3), unknown cause (1)
Ramirez et al.[8] (2014)	Single-blind crossover RCT	69 (38)	65±9	N/A	26±4	PAF (26), PD (12), MSA (21), undetermined (10)
Okamoto et al.[10] (2012)	Single-blind crossover RCT	17 (7)	64±11	N/A	24.9±4.0	PAF (12), PD (5)
Shibao et al.[7] (2007)	Single-blind crossover RCT	21 (12)	62±9 (peripheral) 67±7 (central)	N/A	20±6 (peripheral) 25±4 (central)	Peripheral (11): PAF (8)+PD (3) Central (10): MSA (10)

*We excluded one patient with amyloidosis from this study because they were not consistent with the inclusion criteria; †Mean±standard deviation.
BMI, body mass index; MSA, multiple-system atrophy; N/A, not applicable; PAF, pure autonomic failure; PD, Parkinson's disease; RCT, randomized controlled trial.

Table 2. Primary outcomes of the included studies

Authors (year)	Drug	Change in seated BP at 60 minutes after drug administration (mm Hg)	Change in 1-minute standing BP at 60 minutes after drug administration (mm Hg)	Summary
Okamoto et al.[9] (2019)	Placebo Atomoxetine (18 mg) Pyridostigmine (60 mg) Combination	96±6/61±4→109±6/67±4 91±7/61±5→107±6/68±3 106±8/66±4→99±6/63±4 100±7/62±4→135±10/81±5*	72±8/49±7→72±8/52±4 72±7/53±6→87±11/60±8 74±6/52±5→73±4/53±3 74±6/48±4→97±13/60±7	- Neither atomoxetine nor pyridostigmine increased the seated BP compared with placebo. - The combination significantly increased the seated BP synergistically.
Ramirez et al.[8] (2014)	Placebo Atomoxetine (18 mg) Midodrine (5–10 mg)	N/A 20/10* 20/10*	N/A 20/11* 12/7*	- Atomoxetine and midodrine increased the seated and standing BPs compared with placebo. - Atomoxetine produced a greater pressor response than did midodrine in the standing SBP.
Okamoto et al.[10] (2012)	Placebo Atomoxetine (18 mg) Yohimbine (5.4 mg) Combination	4±17 (SBP) 5±19 (SBP) 7±17 (SBP) 31±33 (SBP)*	1±23 (SBP) 8±16 (SBP) 9±22 (SBP) 28±29 (SBP)	- Neither atomoxetine nor yohimbine significantly increased the seated BP compared with placebo. - The combination significantly increased the seated BP synergistically.
Shibao et al.[7] (2007)	Placebo Atomoxetine (18 mg)	2±13 (SBP) in central nOH -1.1±17 (SBP) in peripheral nOH 54±26 (SBP) in central nOH* 4±18 (SBP) in peripheral nOH	2±17 (SBP) in central nOH 0.6±8 (SBP) in peripheral nOH 45±23 (SBP) in central nOH* 5±11(SBP) in peripheral nOH	- In patients with central autonomic failure, atomoxetine acutely increased seated and standing SBPs compared with placebo. - In patients with PAF, atomoxetine did not elicit a pressor response on seated and standing SBP.

*$p<0.05$.
BP, blood pressure; nOH, neurogenic orthostatic hypotension; PAF, pure autonomic failure; SBP, systolic blood pressure.

SBP by 20 mm Hg (95% CI=14 to 27 mm Hg, p<0.001) and the standing SBP by 20 mm Hg (95% CI=13 to 27 mm Hg, p<0.001) compared with placebo. There was no significant difference between atomoxetine and midodrine treatments for patients regarding the seated SBP (mean difference=0.3 mm Hg, 95% CI=-7.3 to 7.9 mm Hg, p=0.94). However, atomoxetine improved the standing SBP to a greater extent than did midodrine (mean difference=0.4 mm Hg, 95% CI=-3.4 to 4.2 mm Hg, p=0.83). Okamoto et al.[9] found that neither atomoxetine nor pyridostigmine increased the seated SBP. The seated SBP was significantly higher with a combination of atomoxetine and pyridostigmine (135±10 mm Hg, mean± standard deviation) than for placebo (109±6 mm Hg, p<0.001), atomoxetine alone (107±6 mm Hg; p<0.001), or pyridostigmine alone (99±6 mm Hg, p<0.001). Okamoto et al.[10] found that the seated SBP was significantly higher following administration of a combination of atomoxetine and yohimbine than after each drug alone (placebo, p<0.01; atomoxetine, p< 0.001; and yohimbine, p=0.001), whereas the seated SBP after atomoxetine or yohimbine alone did not differ from that after placebo (p>0.05). One common result from the two studies of Okamoto et al.[9,10] was that the seated SBP changed significantly more between baseline and after administration of the drug combination than the sum of the SBP changes produced by the two drugs alone, suggesting a synergistic rather than an additive pressor effect. Shibao et al.[7] compared the efficacy of atomoxetine between patients with central and peripheral autonomic failure. In the former, atomoxetine increased the seated and standing SBPs by 54±26 and 45±23 mm Hg, respectively, at the end of the 60-minute drug trial (compared with increases of 2±13 and 2±17 mm Hg, respectively, with placebo, p=0.004). In contrast, in patients with peripheral autonomic failure, atomoxetine did not induce a pressor effect (changes in seated and standing SBPs of 4±18 and 0.6±8 mm Hg, respectively, compared with -1.1±17 and 5±11 mm Hg for placebo; p=0.695 and p=0.546, respectively).

Effects of atomoxetine on OH-related symptoms

Three of the four included studies evaluated symptoms related to OH using the Orthostatic Hypotension Questionnaire (OHQ)[8-10] (Table 3). The OHQ can be classified into two components: the six-item Orthostatic Hypotension Symptom Assessment (OHSA), which measures the presence and severity of symptoms, and the four-item Orthostatic Hypotension Daily Activity Scale, which measures the impact of orthostatic symptoms on daily activities.[19] Ramirez et al.[8] found that atomoxetine significantly improved OH-related symptoms compared with placebo for both the total OHQ score and that for question 1 only (dizziness, lightheadedness, feeling of faintness, or passing out) scores (p=0.02 and p=0.03, respectively). No differences in the total OHQ or question-1 score were observed between the atomoxetine and midodrine

Table 3. Secondary outcomes of the included studies

Authors (year)	Drug	Change in total OHQ score at 60 minutes after drug administration	Change in AUC_{SBP} at 60 minutes after drug administration	Change in AUC_{DBP} at 60 minutes after drug administration	Adverse events
Okamoto et al.[9] (2019)	Placebo	N/A	424±112→546±118	290±82→360±80	N/A
	Atomoxetine (18 mg)	28.0±6.8→19.3±6.1	463±136→619±145	332±106→421±102	
	Pyridostigmine (60 mg)	29.6±5.6→26.9±5.3	438±109→466±110	289±75→321±74	
	Combination	29.2±4.5→19.9±5.0* (compared with baseline)	551±136→779±173* (compared with baseline)	356±89→460±104* (compared with baseline)	
Ramirez et al.[8] (2014)	Placebo	-	N/A	N/A	N/A
	Atomoxetine (18 mg)	-0.7* (compared with placebo)			
	Midodrine (5–10 mg)	-1.0* (compared with placebo)			
Okamoto et al.[10] (2012)	Placebo	N/A	443±443	N/A	N/A
	Atomoxetine (18 mg)	26.9±14.1→24.4±18.3	428±440		
	Yohimbine (5.4 mg)	27.6±12.2→26.4±12.9	570±350		
	Combination	25.3±16.0→15.7±17.9* (compared with baseline)	690±479* (compared with each drug alone)		
Shibao et al.[7] (2007)	Placebo	N/A	N/A	N/A	N/A
	Atomoxetine (18 mg)				

$AUC_{SBP/DBP}$ at 60 minutes after drug administration compared with that at baseline. It was calculated as SBP/DBP multiplied by standing time, which is a composite score that integrates both the standing time and standing SBP/DBP.
*p<0.05.
AUC, area under the receiver operating characteristic curve; DBP, diastolic blood pressure; N/A, not applicable; OHQ, Orthostatic Hypotension Questionnaire; SBP, systolic blood pressure.

groups (p=0.9 and p=0.42, respectively). In a different context, the two studies of Okamoto et al.[9,10] found that the OHSA score did not improve significantly after administering atomoxetine alone. However, the combination of atomoxetine and pyridostigmine or midodrine resulted in a significant improvement in OHSA score at 60 minutes after administration compared with that at baseline.

Safety of atomoxetine

The side effects and adverse events of atomoxetine in patients with nOH were not reported for any of the four included studies. Across all studies, the pressor effects were only assessed within 1 hour of drug administration, meaning that the long-term outcomes of safety (including fall frequency) were not evaluated. Furthermore, BP in a supine position was not measured in any of the studies, despite supine hypertension being one of the most common adverse reactions to OH medications.

Quality assessment

The risks of bias among the four clinical trial studies included in this systematic review are summarized in Fig. 2. The data were appraised with the Cochrane Collaboration RoB2 tool in RevMan (version 5.4.1) to assess the study quality. The Cochrane Collaboration tool for assessing risk of bias was used to make the process clearer and more accurate. Although the selected articles were called RCTs, Fig. 2 shows that there was a high risk of bias in how random sequences were generated in the studies, since the sequence generation was improperly addressed in the design and implementation phases of the four included RCTs.

The bias mostly arose from certain domains in the Cochrane risk-of-bias tool for RCTs, such as bias from the randomization process. Although each article described the study design as a randomized trial, there was no specific procedure or description for the randomization, or there were inapplicable domains in the blinding entries for participants and personnel, blinding of outcome assessments, and other bias domains were blank.

Focus-group discussion with experts

The focus-group discussion was conducted with 22 movement-disorder specialists with experience in managing nOH. The participants had various durations of clinical experience in treating movement disorders (median 9.5 years, range 4–25 years). Table 4 lists the domains with outcomes reported, accompanied by illustrative quotations from the discussion. It was evident from the expert focus group that no single drug had been consistently used to relieve nOH. Although midodrine and droxidopa have been approved by the FDA for nOH management, droxidopa is currently not easily available in Korea. All participants therefore considered midodrine as the first-line therapy. Other medications for nOH such as fludrocortisone, pyridostigmine, and domperidone are often prescribed by experts of movement disorders. The additional theme of atomoxetine as an nOH treatment emerged.

The experts acknowledged that the selective norepinephrine transporter blocker atomoxetine could effectively relieve OH, especially in patients with MSA who have a central autonomic impairment. However, atomoxetine is only covered by the Korean National Health Insurance (NHI) system[20] as a treatment for ADHD, and not for OH. Hence, only 5 of the 22 movement-disorder specialists had tried to manage nOH with atomoxetine. Among them, four experts reported that atomoxetine was effective in relieving nOH, an effect that was especially pronounced in patients with MSA.

None of the five experts that prescribed atomoxetine reported any adverse effects from using it alone. However, one

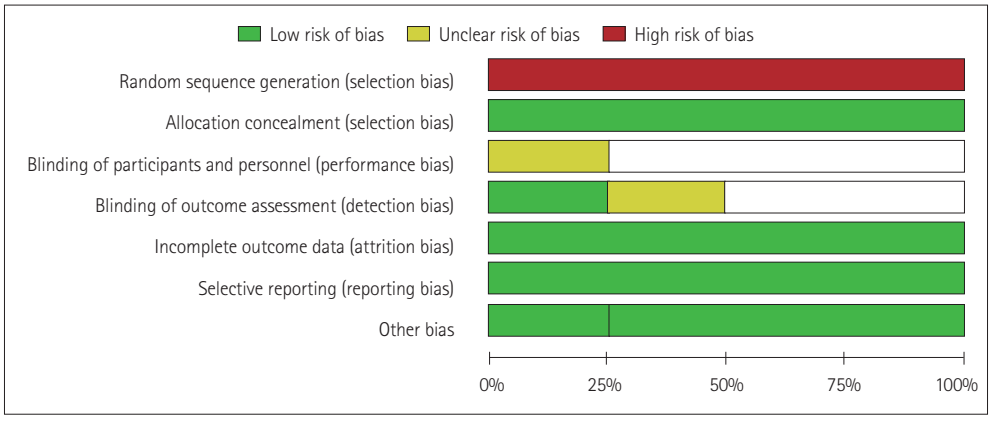

Fig. 2. Summary of the risk of bias in the four clinical trial studies included in the systematic review. Risk of bias was assessed using the Cochrane Collaboration Risk of Bias tool in RevMan (version 5.4.1). There was a high risk of bias in the random sequence generation of the study selection, since the method of sequence generation was inadequately addressed in the design and implementation phases of the randomized controlled trials in the four included data set.

Table 4. Results from the focus-group discussion

Theme	Outcome (*n*)	Example comments
Prior experiences		
General treatment strategy for nOH	Midodrine (22), fludrocortisone (22), pyridostigmine (10), droxidopa (5), domperidone (2)	"We do not have any effective medications for nOH yet."
Atomoxetine for nOH	Effective (4/5) - Especially, in MSA (3/4) Not effective (1/5) No adverse effects (5/5) - But, combined with pyridostigmine, hypertensive crisis occurred (1/5)	
Future expectations		
Atomoxetine for nOH in patients with MSA	Expected, for the first choice (10), expected, but not for the first choice (8), undecided (4)	"After accumulating more clinical experiences, ···" "Coverage by national insurance, price and accessibility are important as well as the efficacy"

MSA, multiple-system atrophy; nOH, neurogenic orthostatic hypotension.

expert reported that a severe hypertensive crisis occurred when using atomoxetine and pyridostigmine together in patients with MSA. Regarding future expectations, 18 of the 22 participants answered that they considered atomoxetine to be a treatment for nOH in patients with MSA, and 10 considered it the first choice. They also emphasized that beyond the efficacy of the drug, it is also important to consider coverage by the NHI system, price, and accessibility.

DISCUSSION

This study utilized innovative data sources and research methods. The data were collected from both research and practice settings, and provided both quantitative and qualitative perspectives on atomoxetine as a treatment for nOH to describe more-dynamic aspects in depth while incorporating evidence-based knowledge. Consistent with the research data and the experiences of experts in our focus-group study, atomoxetine is considered an adequate pharmacological treatment option for relieving orthostatic BP decrease and its symptoms in patients with nOH. The efficacy and safety of atomoxetine might differ between subgroups with central and peripheral autonomic failure or might vary depending on whether the drug is administered alone or in combination with others.

Autonomic dysfunction in synucleinopathies is caused by abnormal intracellular aggregation and deposition of a misfolded α-synuclein in various regions of the central and peripheral nervous systems.[3] Autonomic failure in PD, DLB, and PAF results from the degeneration of peripheral postganglionic noradrenergic fibers.[3] Otherwise, α-synuclein aggregates form glial cytoplasmic inclusions and cause neuronal degeneration in central autonomic pathways, resulting in nOH in MSA.[3] The cardiovagal baroreflex sensitivity in phase IV of the Valsalva maneuver was significantly lower in patients with PD and OH than in those with MSA of Parkinsonian-type OH, indicating a difference between the pathophysiological mechanisms that underly the autonomic dysfunction of the two disorders.[21] It is essential to consider the basic concept of the underlying pathophysiology of nOH when choosing pharmacological treatments.[22] Theoretically, the selective norepinephrine transporter blocker atomoxetine has therapeutic potential in patients with preserved residual endogenous norepinephrine release.[22] Indeed, the pressor effect of atomoxetine was apparent in patients with MSA but not in patients with PD and PAF.[7] In accordance with the findings of the recent retrospective study of Shibao et al.[7] involving 99 patients with nOH, higher supine plasma norepinephrine levels were associated with higher standing BP after atomoxetine administration.[23] Patients with drug-induced parkinsonism also experience autonomic dysfunction.[24] Atomoxetine may be effective in patients with drug-induced parkinsonism, especially in those with increased sympathetic tone due to a psychiatric disorder.[24] In contrast, a predominant increase in BP was found in patients with peripheral sympathetic denervation after the administration of the synthetic norepinephrine precursor droxidopa.[25] Our focus-group data indicated that Korean movement-disorder specialists who have prescribed atomoxetine also reported that its effect in relieving nOH was especially pronounced in patients with MSA.

The practical goal of treating nOH is to improve the standing BP without excessive supine hypertension.[26] Supine hypertension presents in at least 50% of patients with nOH and complicates their management of the condition.[27] An important hypothetical concern about atomoxetine use is the

risk of supine hypertension. However, the supine BP was not assessed in any of the four RCTs[7-10] included in this systematic review. To compensate for this limitation, we included an item about adverse events in the focus-group discussion questionnaire. A daily atomoxetine dose of 18 mg is considered a safe monotherapy regarding the supine hypertension risk. However, the responses from the focus-group discussion raised safety concerns about supine hypertension when using atomoxetine, especially when combined with other pressor agents. Atomoxetine has synergistic effects with medications such as pyridostigmine[9] and yohimbine[10] that can facilitate norepinephrine release in the neurovascular junctions via different mechanisms. Their combination possibly induces and worsens preexisting supine hypertension in patients with nOH. Further research is necessary to determine the long-term safety outcomes of that drug combination.

There is still a lack of evidence on the optimal drug for treating patients with nOH, and selected treatments are therefore largely based on the experience and preference of the individual clinician. We therefore not only conducted a systematic review with a broad search of databases to obtain preliminary insights on the topic, but also an expert focus-group discussion to understand their clinical concerns about the benefits and harms of atomoxetine in nOH management. Moreover, we attempted to conduct a meta-analysis of the four included studies to obtain common primary outcome measures. To this end, we requested raw data from the original authors of the four articles through multiple emails and video conferencing, and these were finally included in the systematic review. However, we could only get raw data from one of the original authors, and a meta-analysis of the data across trials was not possible due to the heterogeneity in the included populations, comparators, and outcome assessment methods.

This review was subject to some limitations: First, few RCTs were included in this systematic review (n=4), and they had small samples and short follow-up periods. The quality of the evidence that supports the results is mostly presented as low or unclear, which indicates that confidence about the effects of atomoxetine is low. Second, the findings from the focus-group discussion by the experts had low generalizability given the small number of participants, who came from a single country with a unique NHI system.

In conclusion, atomoxetine is an effective and safe drug for short-term nOH management, which could possibly be more evident in patients with central autonomic impairment such as MSA. However, these results should be interpreted with caution considering the low quality of the evidence, which was inadequate to verify the efficacy of atomoxetine for long-term use. Further high-quality studies with large samples are therefore necessary to provide future guidance regarding nOH management with atomoxetine. In particular, studies that compare MSA with other α-synucleinopathies including PD and DLB and evaluate the short- and long-term adverse effects of atomoxetine are required in the future.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.0018.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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