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Korean guideline of desmopressin for the treatment of nocturia in men

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Purpose: Nocturia is the most bothersome of lower urinary tract symptoms in men. Desmopressin, a synthetic analog of the human hormone vasopressin, has been used for the treatment of nocturia. However, the guidelines include varying recommendations for the use of desmopressin for the management of nocturia in men. Therefore, the Korean Urological Association (KUA) developed recommendations for desmopressin for the treatment of nocturia in men.

Materials and Methods: A rigorous systematic review was performed and Grading of Recommendations, Assessment, Development, and Evaluation methodology was used to rate the certainty of evidence for patient outcomes and to develop the evidence into recommendations. The steering group, guidelines development group, systematic review team, and external review group consisted of members of the Korean Continence Society, Korean Society of Geriatric Urological Care, and KUA, respectively, who were involved in the guidelines development process.

Results: The guidelines address the benefits, harms, patients' values and preferences, costs, and resources related to desmopressin by using a single clinical question: What is the effectiveness of desmopressin compared to that of placebo, behavior modification, or other pharmacological therapies?

Conclusions: The guidelines development panel suggests desmopressin for men with nocturia instead of placebo, behavior modification, or alpha-blocker monotherapy (low certainty of evidence, weak recommendation). Additionally, the panel suggests desmopressin combination therapy with alpha-blockers for men with nocturia instead of alpha-blocker monotherapy or alpha-blocker combination therapy with anticholinergic agents (low certainty of evidence, weak recommendation).

Keywords: Deamino arginine vasopressin; GRADE approach; Guideline; Men; Nocturia

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INTRODUCTION

Nocturia is a common symptom of the lower urinary tract in adults. Its etiology varies and may include nephrologic causes, hormonal causes, sleep patterns, central nervous system causes, fluid and food intake, concomitant medication use, and overactive bladder [1]. Men with benign prostatic hyperplasia (BPH) may also experience nocturia [2]. Decreased sleep resulting from nocturia has been associated with daytime fatigue, work absenteeism, lower self-rated physical and mental health, and increased rates of nighttime falls and subsequent bone fractures for elderly patients [3,4].

Desmopressin is a synthetic analog of the human hormone vasopressin, which is traditionally used for the treatment of nocturnal enuresis in pediatric patients [5]. Desmopressin is the most frequently used medication for the treatment of nocturia. In 2016, the United States Food and Drug Administration approved desmopressin analogs for the treatment of nocturia caused by nocturnal polyuria [6,7]. Although desmopressin is effective, it is associated with adverse events such as headache, insomnia, dry mouth, hypertension, peripheral edema, nausea, and hyponatremia [8]. Among the medications for the treatment of lower urinary tract symptoms, desmopressin has a 13-fold higher rate of hyponatremia [9].

Urological guidelines include various recommendations for the use of desmopressin for the management of nocturia, probably because of its adverse effects. According to the American Urological Association guidelines, desmopressin is not recommended for patients with nocturia who have already been diagnosed with BPH or overactive bladder [10,11]. Recently, during the American Urological Association 2021 debate session, a panelist mentioned that a complete medical assessment should be performed before using desmopressin for geriatric patients with nocturia caused by nocturnal polyuria [12]. The European Association of Urology (EAU) guidelines suggest desmopressin monotherapy and desmopressin combination therapy with anticholinergics for women with overactive bladder or nocturia caused by nocturnal polyuria [13]. For men with nocturia, the guidelines suggest desmopressin for men younger than 65 years of age with nocturia caused by nocturnal polyuria. However, they suggest low-dose desmopressin for men older than 65 years of age with nocturia at least twice per night caused by nocturnal polyuria [14]. Although the Japanese guidelines do not recommend desmopressin for patients with nocturia [15,16], the International Continence Society recommends desmopressin to treat nocturia caused by BPH [17]. However, there is no consensus regarding the extent of disease severity that warrants treatment [17].

Therefore, the Korean Urological Association (KUA) developed recommendations for desmopressin for the treatment of nocturia in men. To support these recommendations, the guidelines development group performed systematic reviews focused on randomized trials addressing the effects of desmopressin. Based on those systematic reviews, the KUA developed recommendations based on rigorous methodology trustworthiness standards, namely, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [18-21].

MATERIALS AND METHODS

1. Structure of the guidelines team

The steering group, guidelines development group, systematic review team, and external review group, which consisted of members of the Korean Continence Society, Korean Society of Geriatric Urological Care, and KUA, respectively, were involved in the guidelines development process (Supplementary Table 1).

The steering group provided administrative support for guidelines development, determined the scope and key questions of the guidelines, organized the guidelines development group and systematic review team, supervised publication of the guidelines, and oversaw dissemination of the guidelines. The systematic review team drafted the protocols for the systematic reviews, completed the comprehensive literature search and eligibility review, abstracted data, conducted meta-analyses, assessed the risk of bias, and produced summary of finding tables with GRADE certainty of evidence (CoE). The guidelines development group, which included experts in the fields of health research methodology and urology from the medical society, interpreted the evidence with explicit consideration of patient values and preferences, resources, and other practical issues. Then, they formulated recommendations according to GRADE methodology. The external review group, which consisted of two clinical experts, provided suggestions for improving and clarifying the recommended guidelines.

2. Target audience for recommendations

The target subjects for our guidance statement were men who had nocturia and sought medical treatment to relieve their symptoms. Children were excluded from the study. The users of the guidelines included clinical physicians, such as urologists, family physicians, and internists who care for men with nocturia. The guidelines were developed based on

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the best available current evidence to support on-site clinical decision-making between patients and physicians. The guidelines must be flexible with regard to age, comorbidities, and social conditions of the individual patient, as well as the clinical expertise of the physician.

3. Population/patient/problem, intervention, comparison, outcome questions and study eligibility criteria

The guidelines address a single clinical question regarding the benefits, harms, patient values and preferences, costs, and resources related to desmopressin using the following question: What is the effectiveness of desmopressin compared to that of placebo or other pharmacological therapies? The panel of the guidelines development group considered the number of nocturnal voids, quality of life, and major adverse events critically important for developing recommendations. Important outcomes included overall adverse events, urological symptom scores, and duration of the first sleep episode (minutes).

4. Systematic review methods

Systematic reviews were conducted based on a priori methods (CRD42020156252) to inform our recommendations. In consultation with an expert librarian (M.H.K.), a systematic review team searched the major literature databases (Cochrane Library, MEDLINE, EMBASE, Scopus, Google Scholar, Web of Science, and Western Pacific Region Index Medicus) and regional databases (KoreaMed, KMBASE) with no restrictions to the language of publication or publication status until April 7, 2021, to identify all relevant studies of the benefits, harms, patients' values and preferences, costs, and resources regarding the treatment of nocturia in men. The team also searched for clinical trial registries (United States National Institutes of Health Ongoing Trials Register ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform) and grey literature (Opengrey) (Supplementary File). Randomized controlled trials focused on nocturia, defined as one or more voids per night for men, treated using methods such as placebo, alpha-blockers, and anticholinergic agents were included. The review outcomes were the number of nocturnal voids (measured by a voiding diary), quality of life (measured using the International Prostate Symptom Score [IPSS] for quality of life or nocturia quality of life), major adverse events (such as symptomatic hyponatremia, arrhythmia, need for hospital admission, respiratory insufficiency), overall adverse events, urological symptom scores (measured by the IPSS), and duration of the first sleep episode (measured by a voiding diary). The outcomes measured during up to 3 months, during more than 3 months to up to 12 months, and during more than 12 months were defined as short-term, intermediate-term, and long-term outcomes, respectively. Two review authors (J.H.J., E.C.H., H.J.J., and S.H.Y.) participating on a systematic review team independently examined full-text reports, identified relevant studies, and assessed the eligibility of studies for inclusion using reference management software (EndNote) and an online systematic review production toolkit (Rayyan). Two review authors (J.H.J., E.C.H., H.J.J., and S.H.Y.) extracted data using a dedicated data abstraction form and assessed the risk of bias using the Cochrane Risk of Bias assessment tool [22]. Statistical analyses were performed using a random-effects model and Review Manager 5 software (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Heterogeneity was identified through visual inspection of forest plots to assess the amount of overlap of confidence intervals (CIs) and the I^2 statistic, which quantified inconsistencies across studies, to assess the impact of heterogeneity on the meta-analyses [23]. Funnel plots were used to assess publication bias (small study effect) if 10 or more studies were included. The CoE was assessed according to GRADE [18,19]. Any disagreements regarding any step of the systematic review were resolved through discussion and consensus.

5. Moving from evidence to recommendations

The steering group invited potential panel members without perceived conflicts of interest. If important competing issues were identified, then potential panelists were not invited to the guidelines development group. Before our initial guidelines panel meeting, the methodologist and guidelines panel shared the draft questions, received the results of the systematic review, and incorporated feedback. At the initial meeting, the guidelines panel discussed the scope of the project and agreed on the research questions. At three subsequent meetings, the panel developed the recommendations for the guidelines according to GRADE methodology based on systematic reviews in terms of benefits, harms, patients' values and preferences, costs, and resources [20,21].

6. How to interpret the recommendations?

Recommendations for the guidelines were made according to GRADE methodology. The GRADE method classifies each recommendation as strong or weak [19,20].

A strong recommendation is usually supported by moderate to high CoE. A strong recommendation means that the desirable effects of following the recommendation clearly outweigh the undesirable effects (or vice versa); therefore,

Table 1. Summary of recommendation of desmopressin for the treatment of nocturia in men

Recommendation	Certainty of evidence	Strength of recommendation
We suggest desmopressin for men with nocturia compared to placebo or behavior modification only.	Low	Weak
We suggest desmopressin for men with nocturia compared to alpha-blocker.	Low	Weak
We suggest desmopressin combination therapy with alpha-blocker for men with nocturia compared to alpha-blocker monotherapy.	Low	Weak
We suggest desmopressin combination therapy with alpha-blocker for men with nocturia compared to alpha-blocker combination therapy with anticholinergic.	Low	Weak

the course of action would apply to all or almost all patients [19,20].

A weak recommendation is usually supported by low CoE or a close balance between desirable and undesirable effects. A weak recommendation means that the desirable effects of following the recommendation probably outweigh the undesirable effects; therefore, the course of action would apply to the majority of patients, but not all patients [19,20].

Weak recommendations always warrant shared decision-making regarding the choice of treatment for individual patients while considering their values and preferences. Therefore, we used the phrase "we suggest" for weak recommendations rather than "we recommend" or "clinicians should" [19,20].

We used the best available evidence and presented it in a transparent and systematic manner. We have provided a summary of the supporting evidence for each recommendation. When there was no evidence, we indicated and considered a very low CoE according to GRADE methodology [18-20].

7. Updates to guidelines

To keep the guidelines current with the best available evidence, the guidelines development group decided to update the guidelines every 3 to 5 years.

RESULTS

1. Recommendations for desmopressin

We developed four recommendations for desmopressin for the treatment of nocturia in men. However, all recommendations are weak based on the moderate to very low CoE and small magnitude of effect. Table 1 presents the recommendations with the CoE.

2. Evidence summary

Regarding the effects of desmopressin, we found 16 randomized controlled trials involving 3,417 male participants older than 18 years of age with nocturia (Tables 2, 3) [24-39]. The flow of the literature throughout the systematic review process is shown in the PRISMA flowchart (Fig. 1). Seventeen studies did not meet the inclusion criteria or were irrelevant to the trial question. Four studies were classified as awaiting classification (insufficient information for inclusion decision), and one study was ongoing (Supplementary Table 2). All studies were conducted in an outpatient urology clinic setting. Seven trials were multicenter studies [27,30,32,36-39].

The mean age of men in the included studies ranged from 57 to 74 years. The mean baseline IPSS score ranged from 12.1 to 24.9. The mean baseline maximum flow rate ranged from 10.3 mL/s to 17.8 mL/s. One trial reported mean prostate volumes of 45.7 mL for the treatment group and 47.0 mL for the comparator group [24]. Two trials reported the mean prostate-specific antigen level, which ranged from 1.8 ng/mL to 2.6 ng/mL [24,26].

Desmopressin was administered as an oral or sublingual formulation (dissolving tablet) or as a nasal spray. Other treatments compared with desmopressin included placebo, behavior modification alone (liquid restriction during nighttime) [25,30-32,34-39], alpha-blocker monotherapy (alfuzosin, doxazosin, and tamsulosin) [24,26-29], and desmopressin combination therapy with an anticholinergic (solifenacin) [33]. Nine trials [25,30-32,34,36-39] compared desmopressin to placebo and one trial [35] compared desmopressin to behavior modification alone.

Seven studies specified funding sources. Five were supported by pharmaceutical companies [31,32,36,37,39], one was funded by the government [33], and one reported no funding sources [27]. Six studies reported relationships with pharmaceutical companies [25,32,36-39]. Six studies reported no conflicts of interest [24,26,28,30,31,33].

Supplementary Fig. 1 shows the risk of bias of the included studies. The following four comparisons were made and the results were interpreted according to the GRADE narrative statement using a minimally contextualized approach [40,41].

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Table 2. Baseline characteristics of the included studies

Study	Setting	Population					
		N	Inclusion criteria	Age (y)		IPSS	
				Experimental	Control	Experimental	Control
Ahmed et al. (2015) [24]	Outpatient/Egypt	273	People with LUTS/BPH aged ≥50 y with nocturia (≥2 voids/night), nocturnal polyuria (nocturnal urine volume >30% of 24-h urine volume)	70.14±9.27	68.58±10.51	16.78±2.26	17.01±1.99
Cannon et al. (1999) [25]	UK	20	Men aged >50 y with nocturnal polyuria (using 48-h inpatient monitoring or 1-wk frequency volume chart)	NA	NA	NA	NA
Ceylan et al. (2013) [26]	Outpatient/Turkey	31	Men with advanced age, complaints of LUTS and nocturia (≥3 times/night)	57.7±9.8	58.1±7.8	12.1±4.9	14.6±4.3
Kim et al. (2017) [27]	Multicenter/South Korea	109	Men aged 40–65 y with LUTS (IPSS >13), nocturia (≥2 episodes/night), and nocturnal polyuria (NPI >33%)	59.2±5.1	60.3 ± 4.5	24.9±8.2	23.2 ± 6.4
Koca et al. (2012) [28]	Outpatient/Turkey	49	Men aged 50–70 y with LUTS and nocturia (≥2/night)	58.9±7.9	61.7 ± 9.1	17.5±3.9	17.8 ± 3.6
Luo and Xie (2018) [29]	China	34	Men aged ≥40 y with nocturia (≥1 time/night)	65.1±11.2	63.9±9.3	NA	NA
Mattiasson et al. (2002) [30]	Multicenter/Europe, USA	151	Men aged ≥18 y with nocturia (2 voids/night, nocturia index scores >1)	64.5±10.7	65.6±10.2	NA	NA
Rezakhaniha et al. (2011) [31]	Outpatient/single center/Iran	60	Older men (mean age about 63 to 64 y) with voiding ≥2/night	63.33±13.21	64.26±10.46	NA	NA
US Food and Drug Administration (2016) [32]	Multicenter/USA, Canada	1,556/870[a]	Men or women aged ≥50 y with nocturia (≥2 nocturic episodes/night)	66	66	NA	NA
Shin et al. (2014) [33]	South Korea	427	Men aged ≥50 y with LUTS due to bladder outlet obstruction (Qmax ≤15 mL/s, IPSS ≥14) and nocturia (≥1 void/night)	64.6±4.4	66.6±5.4	16.5±4.5	18.0±5.3
Wang et al. (2011) [34]	Single center/Taiwan	126	Men aged ≥65 y with BPH (IPSS >13), nocturia (≥2 voids/night), and nocturnal polyuria (nocturnal urine volume >30%)	73.56±7.71	74.52 ± 5.99	NA	NA
Wang and Chen (2012) [35]	Outpatient/single center/China	60	Older men (age not reported)	NA	NA	NA	NA
Weiss et al. (2012) [36]	Multicenter/Canada, USA	799/416[a]	Men and women aged ≥18 y with nocturia (≥2 voids/night)	NA	NA	NA	NA
Weiss et al. (2013) [37]	Multicenter/Canada, USA	395	Men aged ≥18 y with nocturia (≥2 voids/night)	60.4±12.3	60.8±14.2	NA	NA
Yamaguchi et al. (2013) [38]	Multicenter/Japan	139/54[a]	Men and women aged 55–75 y with nocturia (≥2 voids/night)	NA	NA	NA	NA
Yamaguchi et al. (2020) [39]	Multicenter/Japan	342	Men with ≥2 nocturnal voids (average of 3 d) or more	63.0±12.2	63.2±12.0	NA	NA

Values are presented as mean±standard deviation.
IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; BPH, benign prostatic hyperplasia; NA, not available; NPI, nocturnal polyuria index; Qmax, maximum flow rate.
[a]:Randomized/male.

Table 3. Baseline characteristics of the included studies (continued)

Study	Intervention	Comparator	Outcome	Follow-up
Ahmed et al. (2015) [24]	Desmopressin 60 μg ODT+tamsulosin	Tamsulosin	Primary endpoint: - Number of nocturnal voids Secondary endpoints: - First sleep period - IPSS and QoL scores - Percentage of nocturnal urine volume - Qmax - Adverse effects (reported side effect, blood pressure, body weight, and serum electrolytes)	3 mo
Cannon et al. (1999) [25]	Desmopressin nasal spray 20 μg	Placebo	- Nocturnal frequency - Nocturnal volume - Percentage of urine passed at night (nocturnal volume/24-h urine) - Adverse events	8 wk
Ceylan et al. (2013) [26]	Desmopressin nasal spray 20 μg	Doxazosin	- Number of nocturia - IPSS and QoL score - Qmax - Residual urine - Adverse events	2 mo
Kim et al. (2017) [27]	Desmopressin 0.2 mg oral+alpha-blocker	Placebo+ alpha-blocker	Primary endpoint: - Number of nocturia Secondary endpoints: - Proportion of participants with ≥50% decrease in number of nocturia episodes - Changes in nocturnal urine volume - Nocturnal polyuria index - IPSS - Nocturnal hesitancy score - QoL: International Consultation on Incontinence Questionnaire Nocturia and IPSS-QoL Safety: - Adverse events - Vital signs - Laboratory data	8 wk
Koca et al. (2012) [28]	Desmopressin 0.2 mg oral with alfuzosin	Alfuzosin	- IPSS and QoL score - Qmax - Residual urine - Adverse events	3 mo
Luo and Xie (2018) [29]	Desmopressin 0.2 mg oral	Tamsulosin	Primary endpoint: - Number of nocturia Secondary endpoints: - Hours of undisturbed sleep - Night QoL - QoL Safety: - Adverse events	4 wk
Mattiasson et al. (2002) [30]	Desmopressin 0.1 mg/0.2 mg/0.4 mg oral; dose titration	Placebo	Primary endpoint: - Proportion of participants who had reduction by more than half in the mean number of nocturnal voids after treatment compared with baseline Secondary endpoints: - Number of nightly voids - Duration of sleep period until first void - Nocturnal diuresis - Nighttime/24-h and nighttime/day urine volume - Effect on QoL - Safety of desmopressin treatment (adverse events and serum sodium levels)	3 wk

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Table 3. Continued

Study	Intervention	Comparator	Outcome	Follow-up
Rezakhaniha et al. (2011) [31]	Desmopressin 0.1 mg oral	Placebo	- Number of voids (categorical: <2, 2, and >2 episodes) - Mean number of nocturia - Mean duration of first sleep period - Sleep quality (QoL questionnaire administered by urological societies/categorical: improved and non-improved) - Safety (adverse events)	8 wk
US Food and Drug Administration (2016) [32]	Desmopressin nasal spray 0.75 μg, 1.0 μg, or 1.5 μg	Placebo	Coprimary endpoints: - Change from baseline in the mean number of nocturic episodes per night - Percentage of participants with ≥50% reduction in mean number of nocturic voids per night Secondary endpoints: - Time from when participant went to bed with the intention of falling asleep to first nocturic void (or first morning void in the absence of a nocturic void) - Percentage of nights without nocturic episodes - Percentage of nights with ≤1 nocturic episode - Nocturnal urine volume Safety: - Adverse events	12 wk
Shin et al. (2014) [33]	Desmopressin 0.2 mg oral+tamsulosin	Solifenacin+ tamsulosin	- 3-day voiding diary - IPSS (total and subscore) - Overactive Bladder Symptom Score - Qmax - PVR - Adverse events	8 wk
Wang et al. (2011) [34]	Desmopressin 0.1 mg oral	Placebo	Primary endpoint: - Proportion of participants with reduction by 2 in the mean number of nocturnal voids after long-term treatment vs. baseline Secondary endpoints: - Number of nightly voids - Duration of sleep until the first void (increase of >30 minutes) - Nocturnal volume and nighttime: 24-h urine volume ratio (≤30%) - Effect on QoL - Safety of long-term desmopressin treatment (adverse events and serum sodium levels)	12 mo
Wang and Chen (2012) [35]	Desmopressin 0.1 mg oral	Behavioral modifications	- Nocturia cure rate - Mean number of nocturia - Mean duration of the first period - Sleep quality	8 wk
Weiss et al. (2012) [36]	Desmopressin 10 μg, 25 μg, 50 μg, or 100 μg ODT	Placebo	Coprimary endpoints: - Change from baseline in mean number of nocturnal voids - Proportion of participants with >33% reduction in mean number of nocturnal voids from baseline Secondary endpoints: - Change in diuresis (total and nocturnal volumes) - Change in initial period of undisturbed sleep - Change in nocturia QoL score Safety: - Adverse events - Serum sodium values	4 wk

Table 3. Continued

Study	Intervention	Comparator	Outcome	Follow-up
Weiss et al. (2013) [37]	Desmopressin 50 μg, 75 μg ODT	Placebo	Coprimary endpoints: - Change from baseline in mean number of nocturnal voids - Proportion of 33% responders (participants with a decrease of ≥33% in mean number of nocturnal voids at each visit compared to baseline) Secondary endpoints: - Change from baseline at 3 months in mean number of nocturnal voids - Proportion of 33% responders - Mean time to first void and mean nocturnal urine volume Exploratory endpoints: - Mean self-rated sleep quality - Nocturia QoL - Work productivity and activity impairment percentages Safety: - Adverse events - Serum sodium values	3 mo
Yamaguchi et al. (2013) [38]	Desmopressin 10 μg, 25 μg, 50 μg, or 100 μg ODT	Placebo	Primary endpoint: - Change in mean number of nocturnal voids Secondary endpoints: - Change in initial period of undisturbed sleep - Change in diuresis (nocturnal urine volume) - Change in nocturnal polyuria index - Change in QoL from baseline Safety: - Adverse events - Serum sodium values - Clinical laboratory results (haematology, serum chemistry, and urine analysis), vital signs (diastolic blood pressure, systolic blood pressure, heart rate, and body temperature) and physical exams	3 mo
Yamaguchi et al. (2020) [39]	Desmopressin 25 μg, 50 μg ODT	Placebo	Primary endpoint: - Change from baseline in the mean number of nocturnal voids Secondary endpoints: - Change from baseline in mean time to first awakening to void (first continuous sleep time) - Change from baseline in mean nocturnal urine volume - Change from baseline in mean NPI - Changes in health related QoL, quality of sleep, and level of bother of nocturia Safety: - Adverse events	12 wk

ODT, orally disintegrating tablet; IPSS, International Prostate Symptom Score; QoL, quality of life; Qmax, maximum flow rate; PVR, postvoid residual; NPI, nocturnal polyuria index.

3. Desmopressin compared to placebo or behavior modification alone

1) Short-term outcomes (Supplementary Table 3)

- Number of nocturnal voids: Desmopressin may reduce the number of nocturnal voids (mean difference [MD], -0.55; 95% CI, -0.80 to -0.29; I^2=88%; 7 studies; 2,320 participants; low CoE) [30,32,34,36-39].
- Quality of life (nocturia quality of life based on a scale of 0 to 15 [high score indicates better quality of life]): Desmopressin may result in little to no difference in the quality of life (MD, 1.93; 95% CI, -1.53 to 5.39; 1 study; 334 participants; low CoE) [39].
- Major adverse events: Desmopressin may result in little to no difference in major adverse events (risk ratio [RR], 1.31; 95% CI, 0.30 to 5.82; I^2=38%; 3 studies; 877 participants; low CoE), corresponding to six more events for every 1,000 participants (13 fewer to 89 more events for

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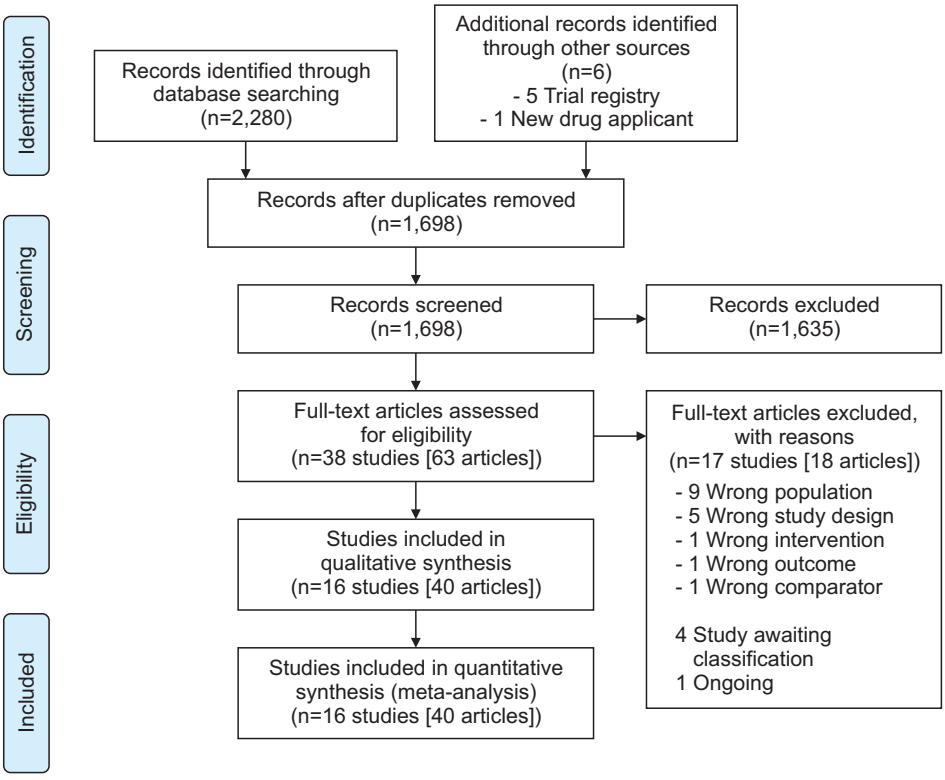

Fig. 1. PRISMA flow diagram.

every 1,000 participants) [30,37,39].

- Overall adverse events: The effect of desmopressin on overall adverse events is uncertain (RR, 0.81; 95% CI, 0.56 to 1.17; I^2=60%; 3 studies; 877 participants; very low CoE). We found 62 fewer events for every 1,000 participants (143 fewer to 55 more events for every 1,000 participants) [30,37,39].
- Urological symptom scores: Not reported.
- Duration of the first sleep episode (minutes): Desmopressin may increase the duration of the first sleep episode (MD, 53.03; 95% CI, 25.62 to 80.44; I^2=90%; 6 studies; 1,050 participants; low CoE) [30,34-36,38,39].

2) Intermediate-term outcomes (Supplementary Table 4) [34]

- Number of nocturnal voids: Desmopressin likely reduces the number of nocturnal voids (MD, -0.85; 95% CI, -1.17 to -0.53; 1 study; 115 participants; moderate CoE).
- Quality of life (increment greater than 2 according to the IPSS for quality of life): Desmopressin likely increases the quality of life (RR, 6.87; 95% CI, 3.60 to 13.11; 1 study; 115 participants; moderate CoE), corresponding to 810 more participants for every 1,000 participants (359 more to 1,670 more participants for every 1,000 participants).
- Major adverse events: Desmopressin may result in little to no difference in major adverse events (RR, 3.05; 95% CI, 0.13 to 73.39; 1 study; 115 participants; low CoE), no adverse events occurred in the control group.
- Overall adverse events: The effect of desmopressin on overall adverse events is uncertain (RR, 0.91; 95% CI, 0.53 to 1.57; 1 study; 115 participants; very low CoE), corresponding to 29 fewer events for every 1,000 participants (154 fewer to 187 more events for every 1,000 participants).
- Urological symptom scores: Not reported.
- Duration of the first sleep episode (minutes): Desmopressin likely resulted in little to no difference in the duration of the first sleep episode (MD, 18.4; 95% CI, 11.6 to 25.2; 1 study; 115 participants; moderate CoE).

3) Desmopressin compared to alpha-blockers (short-term outcomes; Supplementary Table 5)

- Number of nocturnal voids: Desmopressin may result in little to no difference in the number of nocturnal voids (MD, 0.04; 95% CI, -0.55 to 0.62; I^2=53%; 2 studies; 65 participants; low CoE) [26,29].
- Quality of life (IPSS for quality of life based on a scale of 0 to 6 [high score indicates worse quality of life]): The effect of desmopressin on the quality of life is uncertain (MD, 0.04; 95% CI, -0.55 to 0.62; I^2=92%; 2 studies; 65 participants; very low CoE) [26,29].

- Major adverse events: No major adverse events were observed in either study group (2 studies; 65 participants; low CoE).
- Overall adverse events: The effect of desmopressin on overall adverse events is uncertain (RR, 1.71; 95% CI, 0.44 to 6.57; I^2=0%; two studies; 65 participants; very low CoE), corresponding to 65 more events for every 1,000 participants (51 fewer to 506 more events for every 1,000 participants) [26,29].
- Urological symptom scores (IPSS based on a scale of 0 to 35 [high score indicates worse urinary symptom]): Desmopressin may result in little to no difference in urological symptom scores (MD, 0.90; 95% CI, -1.60 to 3.40; 1 study; 31 participants; low CoE) [26].
- Duration of the first sleep episode (minutes): Desmopressin likely increases the duration of the first sleep episode (MD, 84.00; 95% CI, 53.68 to 114.32; 1 study; 34 participants; moderate CoE) [29].

4) Desmopressin combination therapy with alpha-blockers compared to alpha-blocker monotherapy (short-term outcomes; Supplementary Table 6)

- Number of nocturnal voids: Desmopressin plus alpha-blockers may result in little to no difference in the number of nocturnal voids (MD, -0.47; 95% CI, -0.73 to -0.21; I^2=42%; 3 studies; 341 participants; low CoE) [24,27,28].
- Quality of life (IPSS for quality of life): Desmopressin plus alpha-blockers may result in little to no difference in the quality of life (MD, -0.29; 95% CI, -0.51 to -0.07; I^2=0%; 3 studies; 341 participants; low CoE) [24,27,28].
- Major adverse events: Desmopressin plus alpha-blockers may result in little to no difference in major adverse events (RR, 0.30; 95% CI, 0.01 to 7.32; 3 studies; 402 participants; low CoE), corresponding to 3 fewer events for every 1,000 events (5 fewer to 32 more events for every 1,000 participants) [24,27,28]. Only one adverse event in the control group in one study was observed [28].
- Overall adverse events: The effect of desmopressin plus alpha-blockers on overall adverse events is uncertain (RR, 0.69; 95% CI, 0.32 to 1.48; I^2=0%; 2 studies; 154 participants; very low CoE), corresponding to 54 fewer events for every 1,000 participants (118 fewer to 83 more events for every 1,000 participants) [27,28].
- Urological symptom scores (IPSS): Desmopressin plus alpha-blockers likely results in little to no difference in urological symptom scores (MD, -0.41; 95% CI, -0.85 to 0.03; I^2=0%; 3 studies; 379 participants; moderate CoE) [24,27,28].
- Duration of the first sleep episode: Not reported.

5) Desmopressin combination therapy with alpha-blockers compared to alpha-blockers with an anticholinergic (short-term outcomes; Supplementary Table 7) [33]

- Number of nocturnal voids: Desmopressin plus alpha-blockers may result in little to no difference in the number of nocturnal voids (MD, -0.43; 95% CI, -0.97 to 0.11; 1 study; 405 participants; low CoE).
- Quality of life: Not reported.
- Major adverse events: No major adverse events were observed in either study group (1 study; 427 participants; low CoE).
- Overall adverse events: Desmopressin plus alpha-blockers likely results in little to no difference in overall adverse events (RR, 0.22; 95% CI, 0.05 to 0.98; 1 study; 427 participants; moderate CoE), corresponding to 35 fewer events for every 1,000 participants (43 fewer to 1 fewer event for every 1,000 participants).
- Urological symptom scores (IPSS): Desmopressin plus alpha-blocker may result in little to no difference in urological symptom scores: (MD, -2.53; 95% CI, -3.62 to -1.44; 1 study; 405 participants; low CoE).
- Duration of the first sleep episode: Not reported.

4. Balance between desirable and undesirable effects

Across the four comparisons, none of the studies reported a difference in the major adverse event rates. Moreover, six studies reported no major adverse events in the desmopressin group [24,26-29,33]. Although two studies reported that desmopressin or desmopressin combination therapy with alpha-blockers resulted in fewer overall adverse events than other treatments (placebo or desmopressin combination therapy with an anticholinergic) [33,37], other studies reported no difference in the overall adverse event rates.

Although desmopressin may have small effects on relieving nocturia, it can be a treatment option for men with nocturia because of its relatively low incidence of adverse events. However, clinicians should be cautious when prescribing desmopressin to the elderly population because of the increased risk of hyponatremia [8].

5. Values and preferences

Our systematic review found no study of patient values and preferences regarding lower urinary tract symptoms, nocturia, and desmopressin. However, it is well known that

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lower urinary tract symptoms and nocturia negatively affect the quality of life of elderly patients [42]. Nocturia has a significantly higher impact on the quality of life than daytime lower urinary tract symptoms alone. Furthermore, nocturia can cause sleep problems and negatively impact the ability to work [43,44]. The use of medical treatment or physical therapy for nocturia increased with an increase in the frequency of nocturia. Additionally, elderly patients tend to receive treatment related to nocturia more often than younger patients [44]. Therefore, men with nocturia tend to be willing to use medications, namely, desmopressin, to relieve their urinary symptoms.

6. Costs and resources

Our systematic review also did not find any studies of the resource use (e.g., cost) regarding interventions involving desmopressin. In Korea, desmopressin can be easily prescribed by an outpatient clinic if the patient reports nocturia with or without confirmation of nocturnal polyuria by a voiding diary. The cost of desmopressin is relatively inexpensive in Korea, ranging from approximately ₩400 (US$0.3) to ₩1,000 (US$0.8) per pill, and it is covered by the National Health Insurance of Korea. However, a higher proportion of elderly patients are likely to use the medication recommended by the current guidelines, such as alpha-blockers, anticholinergics, and/or beta-3 agonists for the treatment of lower urinary tract symptoms; therefore, we should consider the cost of combination therapy with standard medical therapy [10-15].

7. Rationale for recommendations for desmopressin

The rationale for our recommendations to 'suggest for' rather than 'suggest against' is based on several factors. First, the balance between desirable and undesirable effects favors desmopressin treatment. Desmopressin may reduce the number of nocturnal voids compared with placebo or behavior modification alone (low to moderate CoE). Desmopressin also had a similar effect on the number of nocturnal voids compared with other active treatment modalities (low CoE). The duration of the first sleep episode was longer or often slightly longer in the desmopressin treatment group than in the placebo group (low to moderate CoE). Additionally, desmopressin treatment was associated with similar risks for major and overall adverse events (moderate to very low CoE). Second, costs and resources are not likely to be a barrier for clinicians to prescribe desmopressin. Desmopressin is inexpensive and is covered by the national insurance in Korea. Additionally, the primary care system can effectively respond to a significant number of healthcare demands in Korea. Men with nocturia symptoms can easily access any urology clinic in the community and receive the first consultation at tertiary hospitals. Collectively, the panel of the guidelines development group agreed that these observations warrant weak recommendations for all comparisons.

8. Practical issues and other considerations

Desmopressin, a synthetic analog of arginine vasopressin that increases during sleep, promotes free water conservation, reduces nocturnal urine volume, and has been used for the treatment of nocturnal enuresis and central diabetes insipidus. Based on its mechanism, the primary role of desmopressin is to alleviate nocturnal polyuria [45]. We found four studies that included men with nocturnal polyuria [24,25,27,34]. A subgroup analysis that compared desmopressin to placebo or behavior modification alone in short-term follow-up showed that the MDs in the numbers of nocturnal voids for men with nocturnal polyuria and men with nocturia were -1.28 (95% CI, -1.64 to -0.92) and -0.40 (95% CI, -0.60 to -0.20), respectively; this interaction was significant ($p<0.001$; $I^2=94\%$). When desmopressin combination therapy, with alpha-blockers, was compared to alpha-blockers alone, we found an MD of -0.52 (95% CI, -0.86 to -0.18) for men with nocturnal polyuria and an MD of -0.30 (95% CI, -0.74 to 0.14) for men with nocturia; however, the interaction was not significant ($p=0.44$; $I^2=0\%$). Regarding quality of life, we found an MD of -0.34 (95% CI, -0.67 to -0.01) for men with nocturnal polyuria and an MD of -0.20 (95% CI, -0.84 to 0.44) for men with nocturia; this interaction was not significant ($p=0.71$, $I^2=0\%$). Additionally, there was only one major adverse event in the alpha-blocker group (interaction was not applicable), and the interaction for overall adverse events was not significant ($p=0.42$; $I^2=0\%$). The data showed that there was a tendency for an increased treatment effect of desmopressin on the numbers of nocturnal voids in men with nocturnal polyuria compared to men with nocturia. Although we found subgroup differences in the numbers of nocturnal voids in two comparisons, guideline users should consider that most of the studies included in the systematic review did not provide information about how many participants among men with nocturia had nocturnal polyuria.

BPH is the most common cause of lower urinary tract symptoms in men [46]. While two studies included men with nocturia related to BPH [24,34], we were not able to elucidate the effects of BPH on nocturia in men due to a lack of information regarding the prostate, such as prostate volume and prostate-specific antigen, in the majority of studies. Future studies are needed to find subgroup differences in men

with BPH. However, clinicians should consider that nocturia is often unrelated to the prostate [46].

In addition, the safety issue of desmopressin namely hyponatremia is important to its clinical usage for elderly. Previous review reported the incidence of hyponatremia ranged from 3% to 16% [8]. Although rates of adverse events were similar compared desmopressin to other treatments including placebo (low to very low CoE), care should be taken for elderly patients due to the increased risk of hyponatremia.

DISCUSSION

We developed recommendations for desmopressin following the GRADE Working Group Standards. Based on a systematic review assessing the harms and benefits, the available evidence regarding patients' values and preferences, costs, and resources associated with desmopressin, we suggest desmopressin monotherapy or combination therapy with alpha-blockers for men with nocturia (low CoE, weak recommendation).

1. Why does the panel rate the recommendations as weak?

The weak strength of the recommendations highlights both the small magnitude of desirable effects on the number of nocturnal voids and the duration of the first sleep episode and no difference in the effect or the uncertainty of the effect associated with possible harmful effects. A high patients' preferences for medical treatment for nocturia in elderly patients, and the low cost of desmopressin contributed to a weak recommendation.

2. Comparison with other guidelines

The EAU guidelines suggest desmopressin treatment for nocturia secondary to nocturnal polyuria in men and women after counselling regarding the potential benefits and harms of treatment [13,14]. The recommendation included in our guidelines suggests desmopressin (low CoE and weak strength) and is consistent with the EAU guidelines. Apart from the EAU guidelines, there is still no consensus regarding desmopressin use for men with nocturia. Although the International Continence Society recommends desmopressin for the treatment of nocturia in men with BPH, this recommendation was based on a consensus among experts [16]. Previous studies have found that the effects of desmopressin on nocturnal urine volume reduction were significantly larger for women than for men. Additionally, women were more sensitive to desmopressin than men. Therefore, a lower dose of desmopressin is recommended for women [38,47]. Sex differences in the effect of desmopressin, which are attributable to anatomical differences between men and women, such as the presence or absence of the prostate, could be a causal factor for the small effects on benefits without additional harmful effects. Additionally, the differences in doses and routes of administration among the included studies found during our systematic review may be factors that influence the effects of desmopressin. The guidelines development panel agreed with the EAU guidelines that suggest that desmopressin treatment should be initiated at a low dose and may be gradually increased until maximum efficacy is reached. The actual bioavailability of desmopressin may differ among individual patients.

3. Strengths and limitations

Our guidelines have several strengths. An independent systematic review team conducted the review and meta-analysis according to the rigorous methodology that Cochrane adopted to address evidence from randomized trials regarding desmopressin, and GRADE methodology was used to assess CoE. Furthermore, we searched Korean databases to systematically collect and use desmopressin-related data. We conducted guidelines panel meetings regularly, and they were led by a methodologist (M.A.H.) to derive a recommendation for desmopressin using GRADE evidence.

Our guidelines also have limitations. First, the body of evidence was limited to relatively short-term outcomes. Considering the chronic nature of nocturia symptoms experienced by men, such short-term outcomes are insufficient to assure long-term effectiveness and safety. However, there was scarcity of studies with long-term follow-up over 12 months, both randomized controlled trials and non-randomized studies. Because of the rare incidence of hyponatremia that can cause critical adverse events, including mortality in the elderly population, long-term follow-up data are needed. If we find rigorous observational studies with concurrent comparison groups in terms of rare adverse event related to desmopressin, we will include those as a sequential evidence when updating this guideline. Second, there is a need for clinical trials of desmopressin for men with nocturia, particularly those focusing on nocturnal polyuria and considering the mechanism of desmopressin to reduce urine volume, because the studies found during the systematic review included male participants with nocturia irrespective of etiology. Third, even when searching multiple Korean databases, we found only two studies performed in Korea that focused on the effects of desmopressin combination therapy with alpha-blockers compared with alpha-blocker monotherapy or alpha-blocker combination therapy with an anticholinergic.

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The findings that showed small magnitude or no difference in desirable and undesirable effects were consistent with those from randomized controlled trials performed in other regions. Fourth, the guidelines development group members only consisted of urologists and methodology experts; the panel did not include patients. By reviewing the literature, we tried to reflect patients' values and preferences; however, we did not find any relevant studies. We also did not find any relevant studies regarding the costs and resources.

4. Implications for clinical practice

Desmopressin was approved by the Korea Food and Drug Administration for the treatment of diabetes insipidus and nocturia caused by nocturnal polyuria. Various formulations of desmopressin are available (oral conventional tablets, oral dissolving tablets, and nasal spray). Oral dissolving tablets, which is a water-like formulation that dissolves instantly in the mouth with no need for water, are more suitable for the elderly who may face general difficulties with conventional tablet formulations. Nasal spray, which is a new low-dose formulation of desmopressin and has a greater bioavailability than oral formulations, was approved by the United States Food and Drug Administration in 2017 for the treatment of nocturia due to nocturnal polyuria [13,14]. In Korea, oral conventional tablets (0.1 mg and 0.2 mg) and oral dissolving tablets (25 μg, 50 μg, 60 μg, and 120 μg) are available, but nasal sprays are not [48]. Because the studies included in the systematic review used different types and doses of desmopressin, the types and doses should be prescribed after discussions with patients. Moreover, the use of desmopressin by patients using multiple medications should be considered because this may increase the risk of drug-drug interactions, which may increase serious hyponatremia. BPH is a common medical condition that causes nocturia in aging men and results in a negative impact on public health and a reduction in men's quality of life. While we could not evaluate whether the efficacy of desmopressin differed between men with and without BPH, clinicians should be cautious while prescribing desmopressin to men with BPH given the susceptibility to serious adverse events in the elderly population. Desmopressin is not expensive, but the overall impact on costs incurred by the individual patient is uncertain when the consequences of desirable and undesirable effects are considered. Therefore, we suggest desmopressin for the treatment of nocturia in men (weak recommendation, low CoE).

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20220165.

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