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Comorbidities, Age, and Polypharmacy Limit the Use by US Older Adults with Nocturia of the Only FDA-approved Drugs for the Symptom

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Abstract

Purpose: The goal of this study was to determine if the US adult population with nocturia (waking from sleep at night to void) can easily take medications (desmopressin acetate) approved by the US Food and Drug Administration for nocturia. The study examined: (1) the prevalence of comorbid conditions, laboratory abnormalities, and concomitant medications that increase risk of desmopressin use; and (2) whether these factors are associated with age or nocturia frequency.

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Methods: Using a cross-sectional analysis of four US National Health and Nutrition Examination Survey (NHANES) waves (2005–2012), a total of 4111 participants aged ≥50 years who reported ≥2 nightly episodes of nocturia were identified. The main outcome was frequency of contraindications and drug interactions as described in US Food and Drug Administration–approved prescribing information. These prescribing concerns were matched to examination findings, medical conditions, concomitant medications, and laboratory results of NHANES participants. The associations between prescribing concerns and nocturia severity and age groups were examined.

Findings: The mean participant age was 65.7 years (95% CI, 65.3–66.1), and 45.5% were male. Desmopressin prescribing concerns were present in 80.5% (95% CI, 78.0–82.9) of those ≥50 years of age with nocturia; 50.0% (95% CI, 47.0–53.0) had contraindications, and 41.6% (95% CI, 39.3–44.0) took a concomitant drug that could increase risk of low serum sodium. Desmopressin contraindications were higher with older age ($P < 0.001$) and present in 73.2% (95% CI, 69.3–77.1) of those ≥80 years of age.

Implications: Using NHANES data, this study showed that older US adults with nocturia have a high prevalence of medical conditions, concomitant medications, and baseline laboratory abnormalities that likely increase the risk of potentially severe adverse side effects from desmopressin use. A medication designed and approved for a clinical symptom that is most common in older adults could not be taken by most of the older adults with the symptom.

Keywords

aged or elderly; comorbidity; medications; polypharmacy; risk factors; safety

INTRODUCTION

Nocturia is a symptom defined as waking from sleep at night to void.[1] It independently predicts poor sleep quality.[2] Nocturia is more burdensome if it occurs more frequently[3]; one half of older adults have two or more episodes nightly.[4–6]

Nocturia results from primary sleep disorders, low bladder capacity, and/or increased urine output.[1] Practitioners often address nocturia via treatment of associated conditions such as prostate enlargement, overactive bladder, sleep disorders, or increased urine output. One category of increased urine output is nocturnal polyuria (NP),[7] in which total 24-h urine output is normal but the proportion excreted during nighttime sleep is elevated (≥35%).[1]

Nocturia with NP can be treated with behavioral therapy and/or medications.[8] Arginine vasopressin is a naturally occurring hormone with 2 main functions: (1) to increase the amount of free-water reabsorbed from the renal filtrate back into the circulation; and (2) to increase the peripheral vascular resistance and raise the arterial blood pressure. Desmopressin acetate is a synthetic analogue of vasopressin with reduced blood pressure effects that acts on selective V_2 receptor agonists in renal collecting duct cells.[9] The desired effect with bedtime administration of desmopressin is a higher urine solute concentration (with lower urine output) lasting only during sleep, allowing postponement of voiding. Prompt drug clearance would allow a subsequent compensatory, dilute urine production,

clearing free water and avoiding serum hyponatremia.[10] Older formulations of desmopressin analogues, initially approved in 1978 for adults with central diabetes insipidus,[11] remain available in the United States.[12,13] Past off-label use of older desmopressin formulations for nocturia has been challenging due to serum hyponatremia,[14,15] particularly in older patients.[15,16]

In 2018, the US Food and Drug Administration (FDA) approved 2 new desmopressin acetate formulations, a sublingual tablet17,* and a nasal spray,18,† making these the first drugs indicated for nocturia due to NP.[12] Although these formulations/delivery mechanisms were designed for low, precise dosing,[10] they both carry a boxed warning ("black box warning")[19] regarding potentially severe hyponatremia ("life-threatening, leading to seizures, coma, respiratory arrest, or death").[17,18] The package inserts (ie, prescribing information) describe contraindications, warnings and precautions, and potential drug interactions increasing the risk of low serum sodium ("prescribing concerns") for a range of patient demographic factors, coexisting medical conditions, concomitant medications, and laboratory values. These prescribing concerns determine suitability for treatment initiation (no contraindications) and the need for "more frequent" hyponatremia monitoring. However, the prevalence of prescribing concerns in a population of US older adults with nocturia is unknown.

The purpose of the present analysis was to estimate the prevalence of prescribing concerns for these low-dose desmopressin formulations in adults aged ≥50 years with ≥2 nightly episodes of nocturia and to determine if these prescribing concerns are frequent with older age or more severe nocturia.

SUBJECTS AND METHODS

Participant Data

We used data from the only 4 cycles (2005–2006, 2007–2008, 2009–2010, and 2011–2012) of the US National Health and Nutritional Examination Survey (NHANES)[20] that had questions about nocturia.[5,21] NHANES uses a sampling frame to reach representative populations of non-institutionalized American subjects and oversamples those aged ≥60 years and those who are Black, Asian, and Hispanic. Additional descriptions of the NHANES methods are available elsewhere.[22]

Those ≥50 years of age seen in an NHANES mobile examination center sample (N = 10,560) who responded to the nocturia question (n = 9573) and had ≥2 nightly nocturia episodes (n = 4111) were included in the sample (Fig.). Only adults aged ≥50 years were included because the labeling of one of the two new agents was specific to this age range[18] and also because nocturia is much more common in older adults.[6,23]

We determined that, given this was a retrospective analysis of publicly available, de-identified data, no research review was needed by the Institutional Review Board.

*Trademark: Nocdurna ® (Ferring Pharmaceuticals Inc, Parsippany, New Jersey).
†Trademark: Noctiva ® (Avadel Specialty Pharmaceuticals, LLC, Chesterfield, Missouri).

METHODS

Main Measures

The NHANES nocturia question read: “During the past 30 days, how many times per night did you most typically get up to urinate, from the time you went to bed at night until the time you got up in the morning?” Response categories ranged from 0 to 4, or 5 or more. This question matches validated nocturia surveys[24] and past published NHANES reports.[5]

The main study outcome was frequency of prescribing concerns, a composite outcome including contraindications, warnings and precautions, and drug interactions/more frequent monitoring common in both product labels.[17,18] The majority of prescribing concerns center on increased risk of hyponatremia, and some relate to risk of increased arterial hypertension. We matched specific NHANES variables to co-existing chronic conditions, concomitant medications, vital signs, and clinical laboratory tests described in the package insert in generating prescribing concern estimates (see the Supplemental Table).

Contraindications to using these desmopressin formulations included: reported or diagnosed medical conditions or disorders, such as syndrome of inappropriate antidiuretic hormone secretion (SIADH), congestive heart failure, or uncontrolled hypertension; laboratory-detected hyponatremia (low serum sodium) or renal impairment; concomitant medication use (loop diuretics, or systemic or inhaled corticosteroids); or illnesses causing fluid/electrolyte imbalance, including diarrhea and polydipsia. A self-reported disease status measure[25] was used for heart failure, namely an affirmative response to, “Have you ever been told by a doctor or other health professional that you have heart failure?” Those with a mobile examination center–measured systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg were categorized as having uncontrolled hypertension.[26] Hyponatremia was defined as <134.9 mmol/L.[27–29] We used NHANES data for the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[30] to calculate the estimated glomerular filtration rate (eGFR) for the specified reduced renal function cutoff (ie, eGFR ≤49.9 mL/min/1.73 m^2). A Bristol Stool Scale[31] report of 7 (pure liquid stool)was used to capture episodes of diarrhea.

Warnings or precautions for desmopressin use included a history of urinary retention, risk of fluid retention, or intracranial pressure elevation. We could not identify suitable NHANES variables for these conditions.

Conditions requiring more frequent monitoring of serum low sodium included patient age (≥65 years) and certain concomitant medications. NHANES drug inventories captured all medications and every ingredient in combination medications (eg, Advair Diskus® [GlaxoSmithKline, Research Triangle Park, North Carolina] would be salmeterol and fluticasone).[20] We matched medications in NHANES to the drug classes (thiazide diuretics, selective serotonin reuptake inhibitor [SSRIs], NSAIDs, tricyclic antidepressants, or opioids) mentioned in the prescribing information as use of concomitant drug(s) that could interact and increase the risk of low serum sodium (DILowNa$^+$).

Analysis

Using NHANES sampling weights, US population–based estimates were generated for all calculations. We described frequencies for categorical variables via Rao-Scott χ^2 tests, and continuous variables via means and SDs. The prevalence of prescribing concerns were examined according to nocturia severity (2 vs 3 vs 4 vs ≥ 5 episodes) and by age group (50–64, 65–79, and ≥80 years). SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina) was used for all analyses, and *P* values ≥ 0.05 were considered for statistical significance.

RESULTS

Study Population

Table I presents the demographic and clinical characteristics of the 4111 participants.

Prevalence of Prescribing Concerns

The overall prevalence of prescribing concerns (having any contraindications or requirement for additional monitoring for potential drug interactions or age) was 80.5% (95% CI, 78.0–82.9) (Table II). The prevalence of having at least one contraindication to use of these desmopressin analogues was 50.0% (95% CI, 47–53). The most common contraindications were uncontrolled hypertension (30.4%), taking systemic glucocorticoids and/or inhaled corticosteroids (11.8% and 6.9%, respectively), having reduced renal function (10.6%), taking loop diuretics (8.5%), and reporting congestive heart failure (7.1%). The most common drugs labeled as DILowNa$^+$ were thiazide diuretics (20.1%), NSAIDS (11.8%), opioids (11.1%), and SSRIs (10.2%). Given that some individuals took more than one DILowNa$^+$, the overall prevalence was 41.6% (95% CI, 39.3–44).

Prescribing Concerns and Nocturia Severity

The prevalence of prescribing concerns according to severity of nightly nocturia (2, 3, 4, or ≥5 episodes) is shown in Table II. Overall prescribing concerns and having any contraindication did not differ by nocturia severity. Those with less severe nocturia had a statistically significantly lower frequency of certain contraindications (ie, congestive heart failure, reduced eGFR, diarrhea, taking a loop diuretic, low sodium) compared with those with more severe nocturia but not in a strictly dose-dependent fashion. The overall frequency of DILowNa$^+$s differed according to nocturia severity. Those with less frequent nocturia had a statistically lower frequency of SSRI use ($P = 0.01$) and opioid analgesic use (9.6%, 12.4%, 16%, 16.3% for 2, 3, 4, or ≥5 episodes, respectively; $P = 0.008$).

Prescribing Concerns and Age

Table III describes the prevalence of prescriber concerns according to respondent age group (50–64 years vs 65–79 years vs ≥ 80 years). Overall, having any prescribing concern, any contraindication, and any requirement for frequent monitoring (not including age ≥65 years) was higher in older age groups compared with younger groups. Specific contraindications that were higher in the older groups in a dose-dependent fashion included eGFR ≤49.9 mL/min/1.73 m^2 ($P < 0.001$); uncontrolled hypertension ($P < 0.001$); congestive heart failure ($p < 0.001$); serum sodium <134.9 nmol/L ($P = 0.001$); and taking loop diuretics ($P < 0.001$).

Taking inhaled corticosteroids differed according to age group but not in a dose-dependent fashion ($P = 0.044$). In terms of additional monitoring, those in the older age categories had a dose-dependent higher frequency of thiazide diuretic use ($P < 0.001$) and NSAID use ($P = 0.025$). Only opioid analgesic use was more frequent in younger versus older groups ($P = 0.023$).

DISCUSSION

Four of five adults aged ≥50 years with nocturia have a prescribing concern for using the two low-dose desmopressin analogues approved for nocturia, namely either a contraindication or need for enhanced serum sodium monitoring.[17,18] More than 70% of those aged ≥80 years with nocturia had contraindications to use. Older age group was closely and consistently associated with a higher rate of contraindications and more frequent use of DILowNa$^+$s necessitating additional monitoring for safety.

Use of desmopressin agents is complex, and our study shows that, given the high frequency of prescribing concerns, there is a need for extreme care. Providers must first detect and manage potential causes of nocturia such as diabetes mellitus (found in 24.6% of our sample) or congestive heart failure (7.1%).[11,32] Although not contraindicated by the package inserts, most experts believe uncontrolled diabetes mellitus should preclude desmopressin use.[33] Next, providers should review potentially contraindicating therapy with concomitant medications (eg, loop diuretics, 8.5%; systemic/inhaled steroids, 11.8% and 6.9%, respectively). Past evidence shows that 1 in 8 subjects starting older forms of desmopressin were taking a loop diuretic.[14] As part of an indicated examination,[7] the provider checked blood pressure for uncontrolled hypertension (30.4%). Laboratory studies should be obtained next. Providers must determine the eGFR (insufficient in 10.6%) and verify serum sodium levels (low in 4.6%). Giving older desmopressin formulations to those aged ≥65 years with low baseline serum sodium (≤135 mmol/L) levels resulted in more severe hyponatremia in 3 of 4 clinical trial participants.[16]

Use of newer, low-dose desmopressin formulations in those at higher risk for hyponatremia is impeded by lack of clarity in the monitoring instructions in the package insert. Although the serum sodium check at baseline and the 2 assessments within the first 30 days of therapy are clearly described, ongoing monitoring is to be done “periodically … as clinically appropriate” for those at usual risk and “more frequently” for those at higher risk.[17,18] An expert panel added no clarity, ultimately recommending monitoring to be done “at clinician discretion.”[33] Given that 41.6% of our sample was on at least one concomitant DILowNa$^+$, the lack of a specific recommendation is problematic. Our results are concordant with another study which showed that 50% of those aged ≥60 years started on (older formulations of) desmopressin also received a subsequent DILowNa$^+$ prescription within 30 days.[34]

This analysis focuses on the mismatch between older adults with nocturia and the prescribing instructions for the low-dose agents approved in 2018. However, our concerns are broader than just these 2 specific agents, which is important to note given that one of these agents has already been taken off the market.[18] The 2018 FDA approval led to a tremendous increase in attention to nocturia.[35] Medical references were updated on

use of the new agents.[36] Events, such as Nocturia Awareness Week,[18,37] highlighted to patients and prescribers the problem of nocturia and the availability of specific treatment. Industry advertised to geriatricians, those most likely to care for the very old (≥75 years of age),[38] even though the frail patients for whom they care are poor candidates for therapy.[33] With a high price for these newly approved agents,[12] insurance companies created prior approval pathways in which patients would first be treated with older, higher potency generic desmopressin formulations[39] with similar, or worse, safety profiles but without a boxed warning on hyponatremia.[13] Also, there are novel, nonpeptide agents in development (eg, selective V_2 receptor agonists) that also act as antidiuretic agents to treat nocturia.[40] If newer agents also have the same prescribing concerns as recently approved low-dose desmopressin formulations, most older US adults with nocturia will be unable to safely take them.

Some might argue that concerns about desmopressin in the elderly are well known and already adequately addressed. Desmopressin was identified as a potentially inappropriate medication in adults aged >65 years by the American Geriatrics Society (AGS) in both their 2015[41] and 2019[42] updates to the Beers Criteria. Also, the 2018 FDA-approved desmopressin formulations came with a black box warning, FDA's most stringent caution. We believe that our work adds to these already known cautions. First, Steinman and Fick[43] first emphasize in their editorial accompanying the 2019 AGS Beers Criteria release that the list is of "potentially inappropriate, not definitely inappropriate" medications and that the criteria should be a "starting point for a comprehensive process of identifying and improving medication and safety." Second, we must recognize that many individuals receive medications regardless of black box warnings. Wagner et al[44] reviewed nearly 1 million US patient records examining how 19 selected medications with black box warnings were used. They found that 41.7% of all individuals, and 60% of men and 77% of women aged 75–84 years old, received a medication with a potentially relevant concern related to the black box warning. Also, in 75,000 cases reviewed, only 50% underwent the recommended baseline laboratory studies. Although hundreds of medications might have a reason to carry a black box warning, there are multiple concerns with desmopressin, namely the need for: careful patient selection; baseline and ongoing laboratory screening and monitoring; caution with certain concomitant medications; and additional monitoring for hyponatremia in older men and women.

The present study has several strengths. Our definition of nocturia (≥2 nightly episodes) was based on a standardized question and appropriate for this study. Although the International Continence Society[1,45] counts a single nightly void as nocturia, our ≥2 cutoff matches those recruited to clinical trials[17,18] and are a clinically meaningful level of nocturia.[3] NHANES respondents gave detailed health condition information and provided an inventory of their prescription medications. Also, NHANES oversamples non-White racial and ethnic groups. Therefore, it was possible for us to use sampling weights to adjust back to US population norms and provide estimates of prevalence rates with CIS for prescribing concerns that can be generalized to the noninstitutionalized US population.[46] Our estimates likely provide an underestimate of the true frequency of prescribing concerns. NHANES participants, healthy enough to be a part of a research study, likely had fewer chronic conditions and were on fewer total medications than many older adults. Second, we used 0.0% prevalence

wherever we did not have NHANES data for a condition listed in the package label. Some conditions will be rare (eg, polydipsia, SIADH, risk of increased intracranial hypertension), while others are likely more common (eg, history of urinary retention, fever, infection). We only counted DILowNa$^+$s listed in the package insert, which meant that we did not include the use of agents associated with hyponatremia such as selective serotonin norepinephrine reuptake inhibitors.[47]

The present study has limitations. Our study was cross-sectional, and we cannot assess the incidence of conditions affecting safe desmopressin prescribing. We did not examine prevalence of prescribing concerns for those individuals 18–50 years of age. Although this group of younger individuals will be healthier, they have other potentially relevant concerns that need to be addressed (eg, pregnancy, breastfeeding). We used the FDA-approved prescribing information to be the definitive source of prescribing concerns, yet an expert International Continence Society consensus panel offered an independent and slightly different list of contraindications.[33] Based on their scientific and clinical expertise, the International Continence Society panel differed in opinion from the prescribing information with regard to concomitant diuretic use (ie, thiazide diuretics should instead be a contraindication, loop diuretics would only require monitoring), added some desmopressin contraindications not in the labeling (ie, uncontrolled diabetes mellitus, significant leg edema, older adults that are frail), discounted the significance of some contraindication (ie, a baseline serum sodium level 130–135 mEq/L, concomitant use of inhaled corticosteroids). Given the frequency of several factors that we measured (thiazide diuretics [20.1%], inhaled corticosteroids [6.9%], and loop diuretics [8.5%]), this would not meaningfully change our overall conclusions. Although package inserts requiring baseline laboratory tests may be frequently ignored by providers, we believe that hyponatremia is a legitimate and significant concern. Currently, there are no population-based studies on the frequency of hyponatremia with the 2018 approved desmopressin agents; however, one US study with older desmopressin formulations found a rate of hyponatremia of 146 per 1000 person years.[14] Although hyponatremia may spontaneously occur in older adults, new users of older desmopressin formulations had a hazard ratio of 19.4 (95% CI, 7.1–53.0) compared with propensity score—matched new users of oxybutynin.[14]

Our data source had some limitations for this analysis. Although the NHANES program has data on nocturia, there are no data on NP (nocturia with NP is the FDA-approved indication). Given that NP is extremely common (estimated to be 90%) in older adults with nocturia,[7] the frequency of contraindications and warnings should not differ with respect to NP. We also did not have several items in NHANES relevant to the package insert criteria (ie, polydipsia, SIADH, risk of increased intracranial hypertension, history of urinary retention, fever, infection) or expert panel (ie, significant leg edema, frailty).[33]

Our study did not consider the complexity of the labeling instructions from the patient's perspective in this analysis. Several important patient safety instructions unique to the use of desmopressin might be difficult for a population with cognitive impairment or low health literacy. With one formulation, patients must limit fluid intake (1 h before dosing to 8 h after); also, starting dosages differ by sex.[17] Upward titration of the nasal spray (from 0.83 to 1.66 μg) cannot be done by giving 2 administrations as this delivers more than a 1.66

μg dose.[18] In this analysis, we did not capture all potential possible errors in the use of these drugs. Difficulties in the manufacture of these agents, particularly errors that lead to a higher than specified concentration of desmopressin acetate (superpotency), could also result in higher rates of hyponatremia.[48]

Although we recognize that our findings require validation, we offer for consideration 4 suggestions to improve care and medication safety. First, there are relevant clinical strong practice models that lead to reduced prescribing of potentially inappropriate medications in older patients. These approaches use multicomponent, multilevel interventions: providing didactic education; integrating tailored, electronic medical record decision support tools and environmental cues (eg, pocket cards, stickers) that enhance safer prescribing; and providing 1:1 direct feedback[49] or dashboards[50] on frequency of Beers Criteria drug prescribing. Second, we must address current practices that lead to disregard[44] of FDA black box warnings. As with these desmopressin formulations, the FDA can issue a black box warning upon initial approval, yet they may frequently be issued during postmarketing prescribing.[51] An embedded electronic medical record tool that alerts to relevant, updated, patient-specific information would help. Ironically, in popular parlance, a “black box” is something in which the inside contents are mysterious to the user. Perhaps black box warnings should more explicitly grade the mechanism (eg, idiosyncratic, allergic, pharmacologic property of the drug), probability, and severity of potential harm as well as the strength of evidence underlying the warning. Third, prescribing information often groups those ≥65 years of age into a single category even though those aged 65–74 years are often distinctly different from those aged >80 years. While AGS Beers Criteria listed drugs are only identifying “potentially inappropriate medications”, one could assess desmopressin use just simply on the prevalence of contraindications to be “possibly inappropriate” in those aged 50–64 years (and “likely inappropriate” and “very probably inappropriate” for those aged 65–79 years and those aged ≥80 years, respectively). Finally, study sponsors should be required to prove to the FDA that their recruited research participants reasonably match the population that has the condition of interest. The possibility of such a federal standard is not difficult to imagine. The National Institutes of Health has made such requirements for research enrollment and retention of individuals’ representative of those with the disease[52] so that studies are applicable to those with the condition.[53]

CONCLUSIONS

Overall, in this analysis of a nationally representative sample of adults aged ≥50 years reporting ≥2 episodes of nocturia from four NHANES waves, 80.5% had prescribing concerns. The prevalence of contraindications for desmopressin varied by age and was 37.3% for those aged 50–64 years, 57.6% for those aged 65–79 years, and 73.2% for those aged ≥80 years. This finding highlights the tremendous difference between participants enrolled in clinical trials and the general population with nocturia. Past community prescribing practices have not shown attention to prescribing concerns, as evidenced by the high concomitant use of DILowNa^{+}s. If those in pharmaceutical clinical trials meaningfully differ from the general population with the condition, the benefits and risks of use could be much higher than estimated in clinical trials.[54]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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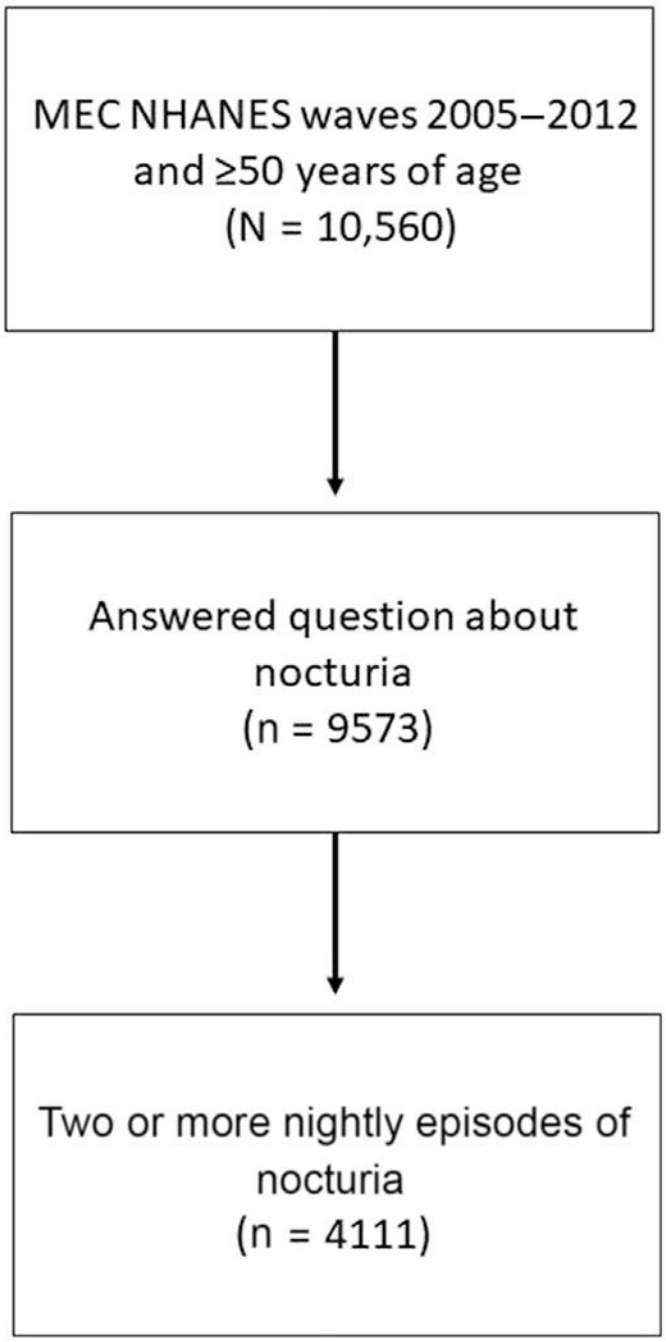

Figure.
Flow diagram of participants in the study. MEC = mobile examination center; NHANES = US National Health and Nutrition Examination Survey.

Table I.

US adults aged ≥50 years with ≥2 episodes of nocturia (sampling weight-adjusted).

Characteristic	N	Mean (SD) or %*	95% CI Around Point Estimate
Demographic characteristics			
Age, y	4111	65.7 (0.2)	65.3–66.1
Age group			
50–64 y	1778	48.4	46.1–50.7
65–79 y	1647	37.2	35.5–38.9
≥80 y	686	14.4	12.9–15.9
Female sex	2060	54.5	52.6–56.4
Race/ethnicity			
Non-Hispanic White	1886	72.9	68.7–77.0
Non-Hispanic Black	1073	13.3	10.6–16.1
Mexican American	605	5.7	3.8–7.5
Other Hispanic	346	3.8	2.7–4.9
Other race*	201	4.4	3.2–5.5
Clinical characteristics			
Nocturia, episodes/night			
2	2346	60.4	58.6–62.2
3	1146	27.4	25.7–29.1
4	381	7.5	6.5–8.5
≥5	238	4.7	4.0–5.5
Serum sodium ≤134.9 mmol/L	177	4.6	3.6–5.5
Congestive heart failure	319	7.1	6.0–8.2
eGFR* ≤49.9 mL/min/1.73 m^2	461	10.6	9.6–11.5
Uncontrolled hypertension†	1403	30.4	27.9–33.0
Systolic BP, mm Hg	3816	132.6 (0.6)	131.4–133.7
Diastolic BP, mm Hg	3816	69.7 (0.3)	69.0–70.3
Diabetes	1167	24.6	22.9–26.4
Depression	1247	29.8	27.8–31.8
Diarrhea Bristol Stool Scale 7	53	1.1	0.6–1.6

Characteristic	N	Mean (SD) or %*	95% CI Around Point Estimate
Drug interaction increasing risk for low serum sodium DILowNa+			
Loop diuretic	376	8.5	7.3–9.6
NSAID‡	540	11.8	10.2–13.4
Systemic glucocorticoids	130	2.8	2.1–3.4
Inhaled corticosteroids	239	6.9	5.7–8.1
SNRI	85	3.3	2.4–4.2
SSRI	357	10.2	8.9–11.5
Tricyclic antidepressant	89	2.7	2.0–3.4
Thiazide diuretic	852	20.1	18.2–21.9
Opioid analgesic	435	11.1	9.5–12.8
Carbamazepine	16	0.3	0.0–0.2
Lamotrigine	6	0.1	0.0–0.2
Chlorpromazine HCl	1	0.1	0.0–0.2
Chlorpropamide	1	<0.1	–

BP = blood pressure; DILowNa+ = drug interaction increasing the risk of low sodium; eGFR = estimated glomerular filtration rate using CKD-EPI; HCl = hydrochloride; NHANES = US National Health and Nutrition Examination Survey; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

*Percentages are based on weighted frequencies.

†Defined as ≥140 mm Hg systolic BP or ≥90 mm Hg diastolic BP.

‡Given by prescription.

Table II.

Prescribing concerns according to nocturia severity (point estimate with 95% CI).

Prescribing Concern	No. of Episodes of Nocturia*				*P*	Overall
	2 (n = 2346)	3 (n = 1146)	4 (n = 381)	≥5 (n = 238)		≥2 (N = 4111)
Any contraindication	48.5%	52.5%	52.0%	51.7%	0.34	50.0%
	45.1–52.0	47.6–57.4	44.0–60.1	44.2–59.3		47.0–53.0
Low GFR†	9.2%	12.2%	15.4%	11.2%	<0.01	10.6%
	7.9–10.4	10.2–14.2	10.2–14.2	7.1–15.4		9.6–11.5
Uncontrolled hypertension‡	30.5%	30.6%	30.0%	29.7%	1.0	30.4%
	27.3–33.6	26.9–34.3	24.0–35.9	21.9–37.5		27.9–33.0
Congestive heart failure	6.1%	7.8%	12.5%	8.5%	<0.01	7.1%
	4.7–7.5	5.9–9.6	8.1–16.9	4.3–12.7		6.0–8.2
Diarrhea	0.6%	1.7%	1.1%	3.2%	0.001	1.1%
	0.3–1.0	0.6–1.9	0.3–1.9	0.4–6.0		0.6–1.6
Low serum sodium <134.9 mmol/L	6.6%	6.4%	3.7%	5.6%	0.04	4.6%
	4.7–8.6	3.8–9.0	1.3–6.1	1.7–9.4		3.6–5.5
Loop diuretic	7.1%	10.1%	12.2%	10.7%	0.02	8.5%
	5.7–8.5	8.0–12.1	7.4–16.9	5.3–16.1		7.3–9.6
Systemic glucocorticoid	11.0%	12.2%	15.4%	13.6%	0.2	11.8%
	8.9–13.1	9.9–14.5	10.4–20.3	7.8–19.5		10.2–13.4
Inhaled glucocorticoid	5.7%	8.0%	10.0%	10.4%	0.5	6.9%
	4.3–7.2	5.2–10.7	6.2–13.7	4.5–16.3		5.7–8.1
DILowNa+	38.8%	45.3%	48.6%	45.3%	<0.01	41.6%
	36.0–56.3	40.9–49.7	41.4–55.8	37.7–53.0		39.3–44.0
Opioid analgesic	9.6%	12.4%	16.0%	16.3%	<0.01	11.1%
	8.0–11.1	9.0–15.8	10.3–21.7	10.3–21.7		9.5–12.8
Thiazide diuretic	19.3%	22.6%	19.1%	16.7%	0.2	20.1%
	17.2–21.4	18.8–26.3	2.5–14.1	10.4–22.9		18.2–21.9
SSRI	8.6%	11.9%	15.8%	12.2%	0.01	10.2%
	7.0–10.3	8.8–15.0	11.2–20.5	6.3–18.1		8.9–11.5
NSAID	11.0%	12.2%	15.4%	13.6%	0.2	11.8%

Prescribing Concern	No. of Episodes of Nocturia*				*P*	Overall
	2 (n = 2346)	3 (n = 1146)	4 (n = 381)	≥5 (n = 238)		≥2 (N = 4111)
	8.9–13.1	9.9–14.5	10.4–20.3	7.8–19.5		10.2–13.4
Tricyclic antidepressant	3.0%	2.6%	1.3%	1.8%	0.5	2.7%
	1.7–4.2	1.4–3.8	0.1–2.5	0.1–3.6		2.0–3.4
Any contraindication or DILowNa$^+$ or age ≥65 y	79.3%	82.4%	81.9%	82.3%	0.52	80.5%
	76.0–82.3	78.0–86.8	75.5–88.3	75.3–89.3		78.0–82.9

DILowNa$^+$ = drug interaction increasing the risk of low sodium; GFR = glomerular filtration rate using CKD-EPI; HCl = hydrochloride; NHANES = US National Health and Nutrition Examination Survey; SSRI = selective serotonin reuptake inhibitor.

Note: Given their low frequency of use (<0.2%) in the sample, we did not include associations of carbamazepine, lamotrigine, and chlorpromazine.

*Point estimates and 95% CIs are based on weighted frequencies.

†Based on Chronic Kidney Disease Epidemiology Collaboration calculation of GFR ≤49.9 mL/min/1.73 m^2.

‡Defined as ≥140 mm Hg systolic blood pressure or ≥90 mm Hg diastolic pressure.

Table III.

Prescribing concerns according to patient age (point estimate with 95% CI).

Prescribing Concern	Age Group*			*P*	Overall
	50–64 y (n = 1778)	65–79 y (n = 1647)	≥80 y (n = 686)		≥50 y (N = 4111)
Any contraindication	37.3%	57.6%	73.2%	<0.001	50.0%
	33.5–41.2	54.0–61.2	69.3–77.1		47.0–53.0
Low GFR†	2.7%	13.8%	29.2%	<0.001	10.6%
	1.7–3.6	11.0–16.5	25.9–32.6		9.6–11.5
Uncontrolled hypertension‡	23.1%	34.2%	45.3%	<0.001	30.4%
	19.6–26.5	30.7–37.8	41.1–49.4		27.9–33.0
Congestive heart failure	3.7%	9.3%	13.1%	<0.001	7.1%
	2.7–4.7	7.3–11.3	10.0–16.1		6.0–8.2
Diarrhea	0.9%	1.1%	1.6%	0.4	1.1%
	0.3–1.5	0.5–1.8	0.5–2.8		0.6–1.6
Low serum sodium <134.9 mmol/L	3.3%	5.0%	7.8%	0.01	4.6%
	2.1–4.5	3.5–6.6	5.7–9.9		3.6–5.5
Loop diuretic	4.7%	10.5%	15.9%	<0.001	8.5%
	3.1–6.4	8.7–12.2	12.2–19.7		7.3–9.6
Systemic glucocorticoid	11.1%	12.9%	11.3%	0.5	11.8%
	8.3–13.9	10.6–15.2	8.8–13.8		10.2–13.4
Inhaled glucocorticoid	6.8%	7.9%	4.5%	0.04	6.9%
	5.1–8.6	6.0–9.8	3.1–5.9		5.7–8.1
Any DILowNa+	40.3%	43.5%	41.2%	0.3	41.6%
	36.6–44.1	40.3–46.7	37.1–45.3		39.3–44.0
Opioid analgesic	13.0%	9.7%	8.4%	0.02	11.1%
	10.5–15.6	7.4–12.0	5.7–11.1		9.5–12.8
Thiazide diuretic	12.9%	21.5%	22.2%	<0.001	20.1%
	8.7–17.0	16.9–26.1	16.2–28.1		18.2–21.9
SSRI	9.3%	9.2%	6.9%	0.7	10.2%
	6.5–12.0	5.8–12.5	4.0–9.8		8.9–11.5
NSAID	9.7%	14.5%	15.2%	0.3	11.8%

Prescribing Concern	Age Group*			*P*	Overall
	50–64 y (n = 1778)	**65–79 y (n = 1647)**	**≥80 y (n = 686)**		**≥50 y (N = 4111)**
	7.0–12.5	10.5–18.5	10.7–19.8		10.2–13.4
Tricyclic antidepressant	1.3%	2.3%	1.4%	0.5	2.7%
	0.2–2.3	0.9–3.7	0.0–3.2		2.0–3.4
Any contraindication or DILowNa^{+}	58.3%	72.3%	81.7%	<0.001	67.0%
	54.2–62.5	69.4–75.2	78.2–85.3		64.1–70.0
Any contraindication or DILowNa^{+} or age ≥65 y	58.3%	100%	100%	–	80.5%
	54.2–62.5				78.0–82.9

DILowNa^{+} = drug interaction increasing the risk of low sodium; GFR = glomerular filtration rate using CKD-EPI; HCl = hydrochloride; NHANES = US National Health and Nutrition Examination Survey; SSRI = selective serotonin reuptake inhibitor.

Note: Given their low frequency of use (<0.2%) in the sample, we did not include associations of carbamazepine, lamotrigine, and chlorpromazine.

*Point estimates and 95% CIs are based on weighted frequencies.

†Based on Chronic Kidney Disease Epidemiology Collaboration calculation of GFR ≤49.9 mL/min/1.73 m^2.

‡Defined as ≥140 mm Hg systolic blood pressure or ≥90 mm Hg diastolic blood pressure.