Are there potential new therapeutic avenues for treating idiopathic nocturia? ICI-RS 2025

Qi-Xiang Song rex_song918@foxmail.com ORCID: 0000-0001-6393-9275
Department of Urology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Sanjay Sinha drsanjaysinha@hotmail.com ORCID: 0000-0001-7090-2091
Department of Urology, Apollo Hospitals, Hyderabad, India.

Bahareh Vahabi bahareh.vahabi@uwe.ac.uk ORCID: 0000-0002-7186-0943
School of Applied Sciences, University of the West of England, Bristol, UK.

Anthony Kanai ajk5@pitt.edu ORCID: 0000-0003-4780-7592
Department of Medicine, Renal-Electrolyte Division, University of Pittsburgh, Pittsburgh, USA.

Christopher Fry chris.fry@bristol.ac.uk ORCID: 0000-0003-3647-5983
School of Physiology, Pharmacology & Neuroscience, University of Bristol, Bristol, UK.

Pradeep Tyagi tyagip@upmc.edu ORCID: 0000-0001-6586-4545
Department of Urology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

Stefania Musco muscos@aou-careggi.toscana.it ORCID: 0000-0001-5844-5684
Neuro-Urology, Azienda Ospedialiero-Universitaria Careggi, Firenze, Italy.

Dudley Robinson dudley.robinson@nhs.net ORCID: 0000-0002-4879-6672
King's College Hospital, Department of Urogynaecology, London, UK.

Marcus J. Drake marcus.drake@imperial.ac.uk ORCID: 0000-0002-6230-2552
Department of Surgery and Cancer, Imperial College London, Hammersmith Hospital, London, UK.

Paul Abrams Paul.Abrams@bui.ac.uk ORCID: 0000-0003-2776-2200
Bristol Urological Institute, Southmead Hospital, Bristol, UK.

Alan Wein alan.wein@pennmedicine.upenn.edu ORCID: 0000-0002-6910-8656
Desai Sethi Institute of Urology, Miller School of Medicine, University of Miami, Miami, Florida, USA.

Christopher R. Chapple c.r.chapple@sheffield.ac.uk ORCID: 0000-0002-2960-9931
Department of Urology, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Sheffield, UK.

Key words: nocturia, sleep, water reabsorption, bladder, circadian rhythm

Abstract word count: 226 words
Manuscript word count (excluding abstract, tables and references): 3,345 words
Reference number: 72

Abstract

Background: Nocturia is a prevalent condition with systematic etiologies which require multidisciplinary collaborations during diagnosis and management. Here we evaluate current evidence and present unresolved research questions regarding the three key pathophysiological domains of nocturia with respect to a conceptual brain-kidney-bladder axis, namely sleep enhancement, extra-renal water reabsorption and circadian regulation of bladder tissue.

Methods: A Think Tank was convened at the 12th International Consultation on Incontinence Research Society meeting in June 2025, looking at novel therapeutic targets for nocturia. This article synthesizes key deliberations from this meeting session.

Results: The discussion was mainly focused on idiopathic nocturia with an overactive bladder symptom complex or nocturnal polyuria. Firstly, medications and conservative non-drug measures targeting sleep that could potentially improve nocturia were considered. Secondly, investigation of water reabsorption mechanisms within the bladder and the role of small molecule vasopressin receptor type-2 agonists were examined that may provide novel therapeutic options to rectify nocturnal polyuria. Finally, to address circadian misalignments, organ specific chronotherapies, based on abnormal circadian features of bladder tissues that can be curative for nocturia, were discussed.

Conclusions: The evidence indicates that promising therapeutic modalities targeting the regulation of sleep-wake cycles, intravesical water transport mechanisms, and circadian patterns of detrusor activity may offer alternative strategies for managing nocturnal polyuria. However, further mechanistic investigations and randomized controlled trials are required to advance these approaches toward clinical translation.

1. Introduction

The symptom of nocturia, defined by the International Continence Society as "the number of times urine is passed during the main sleep period", is prevalent and can be highly bothersome when more severe. It can impair quality of life, and can be associated with increased morbidity.[1,2] The clinical management of nocturia often poses considerable challenges due to mixed lower urinary tract symptoms (LUTS), complex underlying etiologies, and heterogeneous pathophysiology.

The algorithms for the evaluation and treatment of nocturia exemplifies a personalized and holistic approach.[3,4] It includes the use of a bladder diary to categorize underlying pathophysiological features (the presence of 24 hour polyuria or nocturnal polyuria), enabling categorization and paving the way for tailored treatment strategies. Subsequently, the identification of potentially causative conditions is of paramount importance, as evidenced by the PLanning Appropriate Nocturia Evaluation and Treatment (PLANET) study series, in which sleep disorders, cardiovascular diseases, chronic kidney diseases, endocrine diseases and neurological disorders are verified to be potential contributing factors for nocturia in systematic reviews.[5-9] Therefore, it has been recommended that a global assessment using the “SCREeN” diagnosis algorithm could be efficient for identifying these conditions in urology clinics and working in partnership with multidisciplinary force.[10] For idiopathic cases where these conditions are absent, management shifts to a stepwise approach beginning with behavioral modifications and progressing, if necessary, to pharmacotherapies.

Therapeutic strategies primarily target three key pathophysiological domains with respect to the brain-kidney-bladder conceptual axis, namely optimizing sleep quality, minimizing nocturnal urine production and maximizing functional bladder capacity. Despite a range of available therapeutic options and combination regimens, a significant proportion of patients exhibit suboptimal responses to pharmacological interventions.[11] Even for those who may have achieved statistically significant reductions in nocturnal frequency compared to placebo, these often fail to translate into clinically meaningful improvements in sleep quality or patient-reported satisfaction. Furthermore, the potential for drug-related adverse events presents a clinically relevant concern. For example, although desmopressin (either 25 μg, 50 μg or 75 μg) significantly reduced nocturia episodes versus placebo,[12,13] the incidence of hyponatremia is higher in patients aged >65 years (up to 11%), necessitating cautious patient selection and electrolyte monitoring.[14]

To explore novel therapeutic targets for nocturia, a dedicated Think Tank was convened at the 12th International Consultation on Incontinence Research Society (ICI-RS) meeting in 2025. The aims were to evaluate the feasibility of current pharmacological and behavioral interventions targeting sleep enhancement (the circadian sleep-wake cycle) for nocturia management; to critically examine the evidence supporting extra-renal water reabsorption mechanisms beyond classical renal tubular pathways; and to discuss chronobiological regulation of bladder tissue (specifically circadian clock mechanisms) and its therapeutic potential. This article synthesizes key deliberations from the think tank, by presenting current evidence and unresolved research questions to encourage future investigations. It is our intention to consider potential therapeutic avenues for

idiopathic nocturia co-existing with an overactive bladder symptom complex or nocturnal polyuria, rather than those with poorly controlled causative conditions (such as reduced functional capacity due to chronic retention).

2. Potential interventions targeting sleep quality

Although the definition of nocturia incorporates a need to wake up (for the first time) owing to a desire to void urine rather than due to poor quality sleep, interventions targeting sleep could potentially improve nocturia in patients with or even without insomnia.

Medications that improve nocturia by a mechanism targeting sleep should ideally be suitable for long-term use. Currently, cognitive behavioral therapy is the preferred management for chronic insomnia. When necessary, benzodiazepine agonists, melatonin agonists, and orexin antagonists are approved drugs for management.[15] Although the risk is less with benzodiazepine agonists, drug dependence is a concern with this class of drugs. Evidence on nocturia is chiefly found regarding melatonin, ramelteon (a melatonin agonist), as well as lemobrexant and daridorexant (both are orexin receptor antagonists). (Table 1)

With regard to melatonin, five studies examined patients with nocturia, while one each enrolled men with self-reported insomnia combined with lower urinary tract symptoms.[16-22] The studies included a small number of subjects with diverse clinical characteristics, predominantly recruited men, used varying cutoffs for defining nocturia, and were of

short duration.[23] A modest decrease in nocturia episodes was noted in four studies.[16,17,20,22] A randomized trial in 20 men with bladder outflow obstruction noted a difference in the nocturia responder rate (defined as a reduction of at least 0.5 episodes per night) but no difference in the number of nocturia episodes. Half of the men had nocturnal polyuria and the study defined nocturia as ≥3 episodes.[18]

Three studies examined ramelteon, a long acting melatonin agonist, in men with insomnia and nocturia which noted a decrease ranging from -0.39 to -1.1 episodes per night.[24-26] Togo et al. conducted a prospective study using lemborexant, in which sleep quality was dramatically improved accompanied with a relief of nocturia symptoms (nocturia episodes fell from 4.3 to 2.3, $p<0.001$).[27] In addition, daridorexant was studied in a randomized controlled trial against placebo in a crossover design with 4 weeks exposure to the drug. There was a significant reduction in nocturia episodes and an increase in time to first nocturia episode (representing an uninterrupted sleep period) of 0.6 episodes (95% CI -0.9 to -0.3; $p<0.001$) and 31 minutes ($p=0.0027$) respectively. However, these differences were not significant at 4 weeks.[28]

As to conservative non-drug measures, timed light exposure may act as a chronotherapy, restoring the circadian sleep–wake cycle and relieving nocturia. Epidemiological analyses indicate that individuals who watch television or digital video content for more than five hours per day have an increased likelihood of developing nocturia.[29] The widespread exposure to blue light emitted by electronic devices has prompted investigation into the effects of photopic and melanopic wavelengths on the suprachiasmatic nucleus (SCN).[30]

In healthy human subjects, blue light has been demonstrated to suppress melatonin secretion more strongly than other wavelengths.[31] However, in a randomized, double-blind, cross-over, placebo-controlled trial, the use of blue light LED smartphones at night did not lead to a significant change in serum melatonin and cortisol levels, although it did negatively impact sleep quality and cognitive functions.[31] Furthermore, an experimental animal study revealed that prolonged light exposure impaired circadian behavioral rhythms and SCN astrocytic oscillations in the absence of water channel aquaporin-4 AQP4 expression, suggesting a potential role of light therapy to restore central clock rhythmicity and behavioral patterns.[31] However, whether timed light exposure or reducing blue light irradiance, by either altering the melatonin secretion pattern or improving sleep quality, relieves nocturia remain important questions for future research. Plus, it is equally important that, since chronic users of blue-light-emitting devices often exhibit sedentary habits (with the possibility of lower limb edema not excluded), research must correlate this behavior with the measurement of nocturia volume to identify the exact underlying causes.

Other potential lifestyle and behavioral modifications may include: ambient temperature control to modify bladder function; restricting evening fluid intake to reduce nocturnal diuresis; limiting caffeine and alcohol consumption to minimize bladder hypersensitivity; promoting regular daytime physical activity (such as walking, while avoiding heavy meals and strenuous exercise before bedtime); and incorporating stress-management strategies (such as hypnosis, yoga, and thermoregulation techniques) (Figure 1).[32] For example, in a study from Japan, investigators found that reducing the ambient

temperature during the day increased the odds of developing nocturia at night (OR +1.075, 95% CI 1.026-1.126; p=0.002).[33] However, another randomized trial comparing multicomponent behavioral therapy with or without tamsulosin found no difference in nocturia episodes between the two groups.[34] In this study, the conservative arm combined several interventions making it difficult to draw conclusions regarding the impact of sleep hygiene alone.[34] Therefore, despite these recommendations on behavioral and psychological interventions, the current evidence is largely derived from studies on insomnia, and their impact on nocturia, particularly in individuals affected by both disorders, remains unclear.[35]

In short, these sleep interventions were generally well-tolerated with no reports of increased risk of drug abuse, cognitive decline, or falls. However, the studies were constrained by a small number of subjects and short duration for a therapy that could potentially be used in long-term management. Further research questions include:

- Are there specific clinical characteristics of patients who might be suitable candidates for this intervention? (need clinical trials to reveal predictive factors)
- Can a modality of timed drug administration with circadian-controlled pharmacokinetics be developed, based on the sleep–wake cycle or metabolic oscillations to optimize the efficacy of nocturia treatment? (need pharmacokinetics and behavioral studies on animal models)
- How does light-induced melatonin suppression affect nocturia in terms of age-related variations in nocturnal urine secretion and differential interventional responses to specific light exposure modalities? (need to be investigated in animal models)

- How do the types of light (visible or invisible) and time of exposure differently influence protein expression and signaling in the urothelium, where normal and aberrant filling sensations are understood to arise? (need molecular biology and proteomic studies on animal models)
- Can we use optogenetics to elucidate the neural circuits involved in specific light-induced circadian misalignment that causes nocturia? (need to design implantable optogenetic interfaces and validate through animal model studies and neural network mapping)

3. Potential interventions targeting on renal and non-renal water reabsorption mechanisms

Water reabsorption mechanisms within bladder

An early study in rats observed a reduction of intravesical volume with saline infusion into the bladder, but not with soybean oil, when reaching the micturition threshold, indicating water and electrolyte permeability and oil impermeability of the bladder wall.[36] Clinical observations support the idea of transurothelial absorption of water into systemic circulation. Watanabe and Azuma used overnight transabdominal real-time 3D ultrasound in healthy volunteers and identified transient reductions in bladder urine volume (decreases of up to 150ml per episode, occurring at 1-2 hour intervals) at night without voiding, consistent with systemic water reabsorption from the bladder lumen.[37] More recently, Torimoto et al also confirmed this phenomenon in a separate study, strengthening the evidence that the human bladder itself can contribute to nocturnal homeostasis of plasma volume.[38] While dehydration typically elicits lower urine volume

of higher osmolality,[39] healthy adults choosing to extend their voiding interval from 3 to 5h without water restriction produced a >30% reduction in daily urine volume without a concomitant rise in urine osmolality.[40] Intravesical water reuptake could play a role in reducing nocturnal urine volume and perceptions of bladder filling to avoid nocturia, whereas failure of the reabsorption pathways may potentiate nocturnal polyuria and urinary frequency.

MRI scans (with a 7 Tesla 30-cm AVIII spectrometer) of mice bladders measured water influx from hyperosmolar urine (>400mOsmoles/l) to the isotonic (280mOsmoles/l) extracellular space of urothelium,[41,42] is antithetical to the concept of osmosis for water reabsorption and opposed the dogma of a water-impermeable bladder lining.[43] A viable mechanism for water reabsorption is passive paracellular diffusion across tight junctions, as 27% of the luminal surface, lined by apicolateral umbrella cell borders, is amenable to the size of free and bound water molecules, which diffuse more efficiently with the dilation of intercellular gaps during bladder filling.[41]

The passive diffusion of water from lumen to extracellular space is augmented by the facilitated diffusion of water from extracellular space to intravascular space of capillaries through aquaporin channels in the intermediate urothelium. Aquaporins (AQPs) are a family of water channels that facilitate the transmembrane flux of water and small solutes. Several isoforms are expressed in the human bladder urothelium, with AQP3 most consistently reported, together with AQP4, AQP7 and AQP9, supporting the concept that the bladder has a regulatory capacity for water and solute exchange.[44] Functional

studies in differentiated human urothelial cell cultures demonstrate that hyperosmotic stress increases AQP3 expression and that inhibition of AQPs using mercuric chloride, and reduces both water and urea permeability, providing direct evidence of their physiological role.[45]

The functional consequence of water fluxes across bladder urothelium extends beyond volume homeostasis. Distention of mouse urothelial cells in response to osmotic stress drives ATP release, which activates suburothelial afferents via P2X3 receptors and modulates detrusor excitability during cystometry.[46] In cultured mouse and human urothelial cells, mechanosensitive channels such as TRPV4 and PIEZO1/2 mediate this signaling and AQP-driven changes in urothelial cell tonicity are likely to influence their activity.[47] Thus, AQPs provide a mechanistic link between water handling and detrusor excitability. Establishing whether urothelial AQP expression and activity follow circadian rhythms will be critical to understanding their contribution to nocturnal bladder function and may enable identification of patient subgroups in whom AQP-targeted interventions would be most effective.

Small molecule vasopressin receptor type 2 (VR2) agonists

In healthy individuals, the circadian rhythm of the hypothalamic pituitary axis augments release of arginine vasopressin (AVP or antidiuretic hormone) from the pituitary gland and aldosterone from the adrenal glands at nighttime to reduce diuresis and natriuresis, and facilitate detrusor relaxation through modulating VR receptors in the bladder.[48] This combined with homeostatic inhibition of involuntary detrusor contractions to increase

nocturnal bladder capacity, thereby allows uninterrupted sleep. Nocturia may occur due to multifactorial etiologies involving increased diuresis,[49] natriuresis,[50] non-dipping blood pressure during sleep[51] and detrusor hypersensitivity/overactivity.[52,53]

Presently, the only approved drug to treat nocturia is the vasopressin receptor types 1b/2 (VR1b/VR2) agonist desmopressin (dAVP or Nocdurna), a large molecule (molecular weight = 1069 g/mol *vs.* AVP = 1084 g/mol) peptide AVP analog typically administered as an oral or sublingual tablet. However, the therapeutic profile of dAVP is suboptimal due to its associated risk of hyponatremia and limited applicability in the elderly. Its use is primarily confined to managing nocturnal polyuria. In patients with concurrent nocturnal overactive bladder symptoms, combination pharmacotherapy becomes necessary.

In contrast, one potential alternative to dAVP is VA106483 (fedovapagon), a small molecule (molecular weight=463) VR2 agonist. The pharmacological action of fedovapagon is consistent with VR2 activation, triggering the 3',5'-cAMP/PKA pathway for increased transcription and phosphorylation of AQP2 channels and their embedding into the apical membrane of the renal collecting ducts.[54] The anti-diuretic action of fedovapagon was tested in human subjects in ten completed phase I to III clinical trials between 2008-2018 which ultimately demonstrated a 50% reduction in the number of nocturnal voids in men with LUTS (NCT02637960). While the pharmacokinetic half-life of fedovapagon in humans has not been reported, it is likely longer than dAVP (~2 hrs) and AVP (~15 min) which would prolong its antidiuretic effect during the night if used to treat nocturia. Based on the limited information from clinical trials, side effects of dry mouth,

headache, dizziness were minimal as VR2 is predominately located in the periphery. While hyponatremia is still a concern it may be less severe with correct dosing: this remains to be seen and requires further investigation.[55]

While Vantia Therapeutics, UK, reported that the site of action for fedovapagon was solely on the renal collecting ducts,[56-58] recent studies using mice have demonstrated that it also acts on VR2 receptors present in the bladder wall to initiate solute-free water reabsorption by the bladder.[59] In addition, it also relaxes the detrusor smooth muscle as demonstrated by decreased bladder pressure observed in cystometric studies in which mice were subjective to intravesical filling with soybean oil, a substance that is not reabsorbed.[59] Furthermore, it relieves bladder overactivity in an acrolein-induced cystitis animal model, thus theoretically simultaneously targeting diuresis and nocturnal urgency (unpublished data, personal communication, A. Kanai).

In summary, fedovapagon relaxes the detrusor, dampens overactivity and promotes water reabsorption as a potential multi-action therapeutic agent for patients with nocturia and detrusor overactivity. However, promising data raises further research questions:

- If dAVP stimulates bladder VR2 receptors to promote water reabsorption and treat nocturia, what is a plausible mechanism by which fedovapagon also relaxes detrusor smooth muscle? (need to investigate the changes on mechanosensory molecules, detrusor contractile properties and neurotransmitters in animal models)
- Since fedovapagon relaxes the detrusor, should it be investigated for treating OAB? (need to be validated in both animal model studies and clinical trials)

- How are AQPs in the bladder urothelium regulated under physiological and pathological conditions (e.g. nocturia)? (need to study urothelium specimens from both animal and human)
- Is there a circadian variation in urothelial water/solute transport mechanisms, including AQP expression and activity? (need molecular and cell physiology studies on animal models)
- Does circadian regulation of urothelial AQP expression and activity underlie nocturnal bladder dysfunction, thereby enabling identification of patient subgroups for targeted AQP modulation therapies? (need molecular and behavioral studies on both animal and human)

4. Potential interventions targeting bladder circadian mechanisms

A circadian rhythm is a biological cycle driven by an intracellular molecular clock with a period of approximately 24-hours and generally synchronized to a diurnal night-day (sleep-awake) cycle. It is maintained by primary and secondary intracellular negative feedback loops that influence the transcriptional-transcriptional activity of *clock* and *bmal1* genes.[60] The "master clock" lies in the suprachiasmatic nucleus, within the hypothalamus, that influences the activity of similar clocks in peripheral tissues, including those involved in the storage-micturition cycle.[61]

In principle, reduced bladder wall contractile activity during the sleep phase should increase LUT storage function. Whilst rhythmical changes to agonist-induced contractions have been reported in animal models,[62] no substantial changes to the magnitude of nerve-

mediated contractions were observed;[62,63] similar data from human tissue is lacking. Of interest, the magnitude of spontaneous contractile activity is reduced in the sleep phase[63] and because of mucosal involvement in its generation,[64] implies a role for this tissue in contributing to functional circadian rhythmicity.

The mucosa (urothelium and suburothelium) receives a rich afferent innervation that is activated by distortion of this layer mediated, at least in part, by paracrine urothelial ATP release.[65] Such afferent activity is diminished in the sleep phase,[66] and is mirrored by circadian variability of urothelial ATP release and several preceding stages that link urothelial distortion to such release.[67,68] Knock-out of the *clock* gene (in mice?) abolishes such rhythmical changes, suggesting that the circadian clock regulates the urothelial mechano-transduction pathway, from bladder distension to ATP release, and consequently modulates afferent signaling activity.[67,68]

Under pathophysiological conditions, such functional and translational rhythmicity can be disrupted or abolished, as demonstrated in animal models, including the spontaneously hypertensive rat,[69] and the Dahl salt-sensitive rat.[70] With the latter model, a reduced salt intake partly restores a normal circadian pattern, demonstrating that external cues can resynchronize abnormal rhythms. Such inducing factors vary between different organ systems implying that peripheral clocks in the bladder can be synchronized independently of the central clock in the brain.[71] For example, glucocorticoids shift the time-frame of expression of molecular clock components in the bladder wall but have no effect on hepatocyte activity;[72] activation of local muscarinic and purinergic receptors can also reset

this time-frame.[62]

Therefore, based on the circadian features of bladder tissues, organ specific re-synchronization of the abnormal circadian variabilities could be curative of nocturia episodes attributed to impaired circadian bladder sensitivity and excitability properties. The future potential research questions may include:

- The development and validation of biomarkers that may indicate disruptions of diurnal rhythms in the lower urinary tract. (need to study blood and urine samples from healthy individuals and patients with nocturia)
- To describe mechanosensitive properties of epithelial Na^+ channels and diurnal variation of function. (need molecular and cell physiology studies on animal models)
- To evaluate the relationships between diurnal variations of gene expression, protein transcription and functional expression of physiological pathways underlying filling sensations. (need molecular studies and bladder functional assessment on animal models)
- Is the circadian clock of bladder autonomous or dependent on the endocrine inputs from hypothalamus-pituitary-adrenal gland axis relayed to the urothelium first? (need studies on animal models and cultured isolated bladder)
- Does the urothelium receive chronobiology input through night-time fluctuations in bladder fill rate of urine from kidney in addition to the blood levels of hormones released during sleep? (need to be investigated in animal models)

Conclusions

As discussed above, evidence suggests that promising therapeutic approaches targeting the circadian sleep-wake cycle, intravesical water transport mechanisms (AQPs and VR2) and rhythmic patterns of bladder tissue function, may provide alternative strategies for improving nocturia symptoms. However, several research gaps remain, including, standardizing drug administration and lifestyle modification protocols; investigating the feasibility and safety of small-molecular VR2 agonists in clinical trials; clarifying the physiological and pathological roles of urothelial AQPs; and exploring chronotherapies that target the bladder's peripheral clock to modify storage function according to the circadian rhythm.

Declarations of interest:

Pradeep Tyagi is an inventor of liposome technology licensed to Lipella Pharmaceuticals and consults with Vensica Therapeutics.

Stefania Musco is an honorary speaker of Hollister Italia, Convatec Italia, Teleflex Italia, Bbraun Italia and Ecupharma. She is on the advisory board of Convatec Limited and Pierre-Fabre Italia, and editorial board of Pierre-Fabre Medicament (France).

None of the above is related to this work.

References

1. Hashim H, Blanker MH, Drake MJ, et al. International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. 10.1002/nau.23917. *Neurourol Urodyn*. 2019;38(2):499-508. doi:papers3://publication/doi/10.1002/nau.23917
2. Nakagawa H, Niu K, Hozawa A, et al. Impact of Nocturia on Bone Fracture and Mortality in Older Individuals: A Japanese Longitudinal Cohort Study. 10.1016/j.juro.2010.05.093. *JURO*. 2010;184(4):1413-1418. doi:papers3://publication/doi/10.1016/j.juro.2010.05.093
3. Cornu J-N, Abrams P, Chapple CR, et al. A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management--a systematic review and meta-analysis. 10.1016/j.eururo.2012.07.004. *Eur Urol*. 2012;62(5):877-890. doi:papers3://publication/doi/10.1016/j.eururo.2012.07.004
4. Everaert K, Hervé F, Bosch R, et al. International Continence Society consensus on the diagnosis and treatment of nocturia. 10.1002/nau.23939. *Neurourol Urodyn*. 2019;38(2):478-498. doi:papers3://publication/doi/10.1002/nau.23939
5. van Merode NAM, Dawson S, Coulthard E, et al. Assessment and Treatment of Nocturia in Neurological Disease in a Primary Care Setting: Systematic Review and Nominal Group Technique Consensus. *Eur Urol Focus*. Jan 2022;8(1):33-41. doi:10.1016/j.euf.2021.12.012
6. Papworth E, Dawson S, Henderson EJ, et al. Association of Sleep Disorders with Nocturia: A Systematic Review and Nominal Group Technique Consensus on Primary Care Assessment and Treatment. *Eur Urol Focus*. Jan 2022;8(1):42-51. doi:10.1016/j.euf.2021.12.011
7. Dawson S, Duncan L, Ahmed A, et al. Assessment and Treatment of Nocturia in Endocrine Disease in a Primary Care Setting: Systematic Review and Nominal Group Technique Consensus. *Eur Urol Focus*. Jan 2022;8(1):52-59. doi:10.1016/j.euf.2021.12.008
8. Reyes PBG, Butcher K, Cotterill N, et al. Implications of Cardiovascular Disease for Assessment and Treatment of Nocturia in Primary Care: Systematic Review and Nominal Group Technique Consensus. *Eur Urol Focus*. Jan 2022;8(1):26-32. doi:10.1016/j.euf.2021.12.014
9. Ridgway A, Cotterill N, Dawson S, et al. Nocturia and Chronic Kidney Disease: Systematic Review and Nominal Group Technique Consensus on Primary Care Assessment and Treatment. *Eur Urol Focus*. Jan 2022;8(1):18-25. doi:10.1016/j.euf.2021.12.010
10. Smith M, Dawson S, Andrews RC, et al. Evaluation and Treatment in Urology for Nocturia Caused by Nonurological Mechanisms: Guidance from the PLANET Study. *Eur Urol Focus*. Jan 2022;8(1):89-97. doi:10.1016/j.euf.2022.01.007

11. Sakalis VI, Karavitakis M, Bedretdinova D, et al. Medical Treatment of Nocturia in Men with Lower Urinary Tract Symptoms: Systematic Review by the European Association of Urology Guidelines Panel for Male Lower Urinary Tract Symptoms. 10.1016/j.eururo.2017.06.010. *Eur Urol*. 2017:1-13. doi:papers3://publication/doi/10.1016/j.eururo.2017.06.010
12. Weiss JP, Herschorn S, Albei CD, van der Meulen EA. Efficacy and Safety of Low Dose Desmopressin Orally Disintegrating Tablet in Men with Nocturia: Results of a Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group Study. 10.1016/j.juro.2012.12.112. *J Urol*. 2013;190(3):965-972. doi:papers3://publication/doi/10.1016/j.juro.2012.12.112
13. Sand PK, Dmochowski RR, Reddy J, van der Meulen EA. Efficacy and Safety of Low Dose Desmopressin Orally Disintegrating Tablet in Women with Nocturia: Results of a Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group Study. 10.1016/j.juro.2013.02.037. *J Urol*. 2013;190(3):958-964. doi:papers3://publication/doi/10.1016/j.juro.2013.02.037
14. Juul KV, Malmberg A, van der Meulen E, Walle JV, Norgaard JP. Low-dose desmopressin combined with serum sodium monitoring can prevent clinically significant hyponatraemia in patients treated for nocturia. *BJU Int*. May 2017;119(5):776-784. doi:10.1111/bju.13718
15. Kim WJ, Kim HS. Emerging and upcoming therapies in insomnia. *Transl Clin Pharmacol*. Mar 2024;32(1):1-17. doi:10.12793/tcp.2024.32.e5
16. Leerasiri P, Pariyaeksut P, Hengrasmee P, Asumpinwong C. Effectiveness of melatonin for the treatment of nocturia: a randomized controlled trial. *Int Urogynecol J*. Feb 2023;34(2):485-492. doi:10.1007/s00192-022-05232-3
17. Sugaya K, Nishijima S, Miyazato M, Kadekawa K, Ogawa Y. Effects of melatonin and rilmazafone on nocturia in the elderly. *J Int Med Res*. Sep-Oct 2007;35(5):685-91. doi:10.1177/147323000703500513
18. Drake MJ, Mills IW, Noble JG. Melatonin pharmacotherapy for nocturia in men with benign prostatic enlargement. *J Urol*. Mar 2004;171(3):1199-202. doi:10.1097/01.ju.0000110442.47593.ea
19. Khan R, Uren A, Canham L, Cottrell D, Drake MJ, Cotterill N. What Are the Participants' Perspectives of Taking Melatonin for the Treatment of Nocturia in Multiple Sclerosis? A Qualitative Study Embedded within a Double-Blind RCT. *Mult Scler Int*. 2018;2018:4721505. doi:10.1155/2018/4721505
20. Fotovat A, Samadzadeh B, Ayati M, et al. The effect of Melatonin on Improving the benign Prostatic Hyperplasia Urinary Symptoms, a Randomized Clinical Trial. *Urol J*. Nov 8 2022;19(5):406-411. doi:10.22037/uj.v18i.6761
21. Batla A, Simeoni S, Uchiyama T, et al. Exploratory pilot study of exogenous sustained-release melatonin on nocturia in Parkinson's disease. *Eur J Neurol*. Jun

2021;28(6):1884-1892. doi:10.1111/ene.14774
22. Park MJ, Park, Nam-Cheol, Seoseonyoung, Jun PH, Park JH, Lim MY. Therapeutic Effects of Prolonged Release Melatonin (Circadin®) in Patients with Overactive Bladder and Chronic Insomnia in More Than 55 Years Old. *Kosin Medical Journal*. 2020;35:101-113.
23. Burke CA, Nitti VW, Stothers L. Melatonin and melatonin receptor agonists in the treatment of nocturia: A systematic review. *Neurourol Urodyn*. Apr 2024;43(4):826-839. doi:10.1002/nau.25443
24. Kawahara T, Morita S, Ito H, et al. Ramelteon combined with an alpha1-blocker decreases nocturia in men with benign prostatic hyperplasia. *BMC Urol*. Jun 12 2013;13:30. doi:10.1186/1471-2490-13-30
25. Shimizu N, Sugimoto K, Nozawa M, et al. Efficacy of Ramelteon in Patients with Insomnia and Nocturia. *Low Urin Tract Symptoms*. May 2013;5(2):69-74. doi:10.1111/j.1757-5672.2012.00166.x
26. Shimizu N, Nozawa M, Sugimoto K, et al. Therapeutic efficacy and anti-inflammatory effect of ramelteon in patients with insomnia associated with lower urinary tract symptoms. *Res Rep Urol*. 2013;5:113-9. doi:10.2147/RRU.S44502
27. Togo Y, Kaizuka Y, Nagasawa S, Kajio K, Kondoh N, Taguchi K. Efficacy and Safety of Lemborexant for Insomnia Patients With Nocturia-A Prospective Study. *Low Urin Tract Symptoms*. Nov 2024;16(6):e12534. doi:10.1111/luts.12534
28. Lederer K, Benes H, Fine A, et al. A randomised crossover trial of daridorexant for the treatment of chronic insomnia and nocturia. *J Sleep Res*. Mar 13 2025:e70002. doi:10.1111/jsr.70002
29. Wang J, Zhang A, Ye M, Zhang C. Association between TV and/or video time and nocturia in adults: An analysis of the National Health and Nutrition Examination Survey. *Neurourol Urodyn*. Mar 2024;43(3):628-637. doi:10.1002/nau.25406
30. Wahl S, Engelhardt M, Schaupp P, Lappe C, Ivanov IV. The inner clock-Blue light sets the human rhythm. *J Biophotonics*. Dec 2019;12(12):e201900102. doi:10.1002/jbio.201900102
31. West KE, Jablonski MR, Warfield B, et al. Blue light from light-emitting diodes elicits a dose-dependent suppression of melatonin in humans. *J Appl Physiol (1985)*. Mar 2011;110(3):619-26. doi:10.1152/japplphysiol.01413.2009
32. Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. Feb 1 2021;17(2):255-262. doi:10.5664/jcsm.8986
33. Saeki K, Obayashi K, Kurumatani N. Indoor cold exposure and nocturia: a cross-sectional analysis of the HEIJO-KYO study. *BJU Int*. May 2016;117(5):829-35. doi:10.1111/bju.13325

34. Johnson TM, 2nd, Vaughan CP, Goode PS, et al. Pilot Results from a Randomized Trial in Men Comparing Alpha-Adrenergic Antagonist versus Behavior and Exercise for Nocturia and Sleep. *Clin Ther*. Oct 28 2016;doi:10.1016/j.clinthera.2016.10.001
35. Tyagi S, Resnick NM, Perera S, Monk TH, Hall MH, Buysse DJ. Behavioral treatment of chronic insomnia in older adults: does nocturia matter? *Sleep*. Apr 1 2014;37(4):681-7. doi:10.5665/sleep.3568
36. Sugaya K, Ogawa Y, Nishizawa O, de Groat WC. Decrease in intravesical saline volume during isovolumetric cystometry in the rat. *Neurourol Urodyn*. 1997;16(2):125-32. doi:10.1002/(sici)1520-6777(1997)16:2<125::aid-nau6>3.0.co;2-g
37. Watanabe H, Azuma Y. Periodical measurement of urine volume in the bladder during sleep: Temporary volume reduction suggestive of absorption. *Int J Urol*. Feb 2016;23(2):182-7. doi:10.1111/iju.12999
38. Torimoto K, Matsushita C, Itami Y, et al. Assessment of bladder function for stabilizing urinary volume overnight with recording of brain waves (ABSORB study). *Low Urin Tract Symptoms*. Jan 2022;14(1):72-77. doi:10.1111/luts.12412
39. Morgan JE, Dunning ON, Tocci ND, Mauney EL, Yazell AS, Rogatzki MJ. Plasma and serum volume remain unchanged following a 12-h fast from food and drink despite changes in blood and urinary hydration markers. *Eur J Clin Nutr*. Mar 2025;79(2):161-167. doi:10.1038/s41430-024-01526-5
40. Fry C, Tasman K, Goodhead L. Salt and water transport across the human bladder wall. *Continence*. 2023/09/01/ 2023;7:100812. doi:https://doi.org/10.1016/j.cont.2023.100812
41. Tyagi P, Ganguly A, Foley L, et al. Why " Water-tight" Bladder is Averse to Osmosis But Amenable To Diffusion ? *Continence*. 2024/10/01/ 2024;12:101427. doi:https://doi.org/10.1016/j.cont.2024.101427
42. Oe H, Yoshiki H, Zha X, et al. Urinary reabsorption in the rat kidney by anticholinergics. *Sci Rep*. Apr 28 2021;11(1):9191. doi:10.1038/s41598-021-88738-y
43. Romih R, Korosec P, Jezernik K, et al. Inverse expression of uroplakins and inducible nitric oxide synthase in the urothelium of patients with bladder outlet obstruction. *BJU Int*. Apr 2003;91(6):507-12. doi:10.1046/j.1464-410x.2003.03052.x
44. Rubenwolf PC, Georgopoulos NT, Clements LA, et al. Expression and localisation of aquaporin water channels in human urothelium in situ and in vitro. *Eur Urol*. Dec 2009;56(6):1013-23. doi:10.1016/j.eururo.2008.08.013
45. Rubenwolf PC, Georgopoulos NT, Kirkwood LA, Baker SC, Southgate J. Aquaporin expression contributes to human transurothelial permeability in vitro and is modulated by NaCl. *PLoS One*. 2012;7(9):e45339. doi:10.1371/journal.pone.0045339

46. Burnstock G. Purinergic signalling in the urinary tract in health and disease. *Purinergic Signal*. Mar 2014;10(1):103-55. doi:10.1007/s11302-013-9395-y
47. Miyamoto T, Mochizuki T, Nakagomi H, et al. Functional role for Piezo1 in stretch-evoked Ca(2)(+) influx and ATP release in urothelial cell cultures. *J Biol Chem*. Jun 6 2014;289(23):16565-75. doi:10.1074/jbc.M113.528638
48. Ikeda Y, Zabbarova I, de Rijk M, et al. Effects of vasopressin receptor agonists on detrusor smooth muscle tone in young and aged bladders: Implications for nocturia treatment. *Continence (Amst)*. Jun 2022;2doi:10.1016/j.cont.2022.100032
49. Goessaert AS, Krott L, Hoebeke P, Vande Walle J, Everaert K. Diagnosing the pathophysiologic mechanisms of nocturnal polyuria. *Eur Urol*. Feb 2015;67(2):283-8. doi:10.1016/j.eururo.2014.09.003
50. Natsume O, Nishimura N, Shimizu T, Fujimoto K. Night-to-Day Ratio of Excreted Urinary Sodium Concentration Using Spot Urine in Older Adults With Nocturnal Polyuria. *Neurourol Urodyn*. Apr 2025;44(4):716-721. doi:10.1002/nau.25670
51. Kato Y, Akaihata H, Takezawa K, et al. Association between nocturnal polyuria and 24-h blood pressure fluctuations in males with lower urinary tract symptoms: A multicenter prospective study. *Int J Urol*. Mar 2024;31(3):259-264. doi:10.1111/iju.15354
52. Monaghan TF, Bliwise DL, Suss NR, et al. Overnight Urge Perception in Nocturia Is Independent of Depression, PTSD, or Anxiety in a Male Veterans Administration Population. *J Clin Sleep Med*. Apr 15 2019;15(4):615-621. doi:10.5664/jcsm.7726
53. Abu Mahfouz I, Asali F, Abdel-Razeq R, et al. Bladder sensations in women with nocturia due to overactive bladder syndrome. *Int Urogynecol J*. May 2020;31(5):1041-1048. doi:10.1007/s00192-020-04257-w
54. Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. *Nat Rev Nephrol*. Oct 2015;11(10):576-88. doi:10.1038/nrneph.2015.89
55. Andersson KE, Van Kerrebroeck P. Pharmacotherapy for Nocturia. *Curr Urol Rep*. Feb 9 2018;19(1):8. doi:10.1007/s11934-018-0750-y
56. Golor G, McElwaine-Johnn H, Handy R, Yea C, Lambert J. Administration of Fedovapagon Causes a Dose-Responsive Reduction in Nocturnal Polyuria Index. *J Urology*. Apr 2013;189(4):E930-E931. doi:DOI 10.1016/j.juro.2013.02.2199
57. McElwaine-Johnn H, Golor IG, Handy R, Yea C, Lambert J. Antidiuretic Effect of Fedovapagon in Older Males with Benign Prostatic Hyperplasia and Nocturia. *Neurourol Urodyn*. Aug 2013;32(6):906-907. doi:10.1002/nau.22472
58. McElwaine-Johnn H, Schultz R, Yea C, Leese P. The Antidiuretic Effect of Fedovapagon Can Be Effectively Controlled By Dose. *Neurourol Urodyn*. Aug 2013;32(6):820-821. doi:10.1002/nau.22472

59. Zabbarova I, Ikeda Y, Tyagi P, et al. Localized activation of vasopressin receptor 2 by small molecule agonist, fedovaptagon, induces bladder relaxation and urine reabsorption in mice. *Continence*. 2025/01/01/ 2025;15:102189. doi:https://doi.org/10.1016/j.cont.2025.102189
60. Patke A, Young MW, Axelrod S. Molecular mechanisms and physiological importance of circadian rhythms. *Nat Rev Mol Cell Biol*. Feb 2020;21(2):67-84. doi:10.1038/s41580-019-0179-2
61. Noh JY, Han DH, Kim MH, et al. Presence of multiple peripheral circadian oscillators in the tissues controlling voiding function in mice. *Exp Mol Med*. Mar 7 2014;46(3):e81. doi:10.1038/emm.2013.153
62. Wu C, Sui G, Archer SN, et al. Local receptors as novel regulators for peripheral clock expression. *FASEB J*. Nov 2014;28(11):4610-6. doi:10.1096/fj.13-243295
63. White RS, Zemen BG, Khan Z, Montgomery JR, Herrera GM, Meredith AL. Evaluation of mouse urinary bladder smooth muscle for diurnal differences in contractile properties. *Front Pharmacol*. 2014;5:293. doi:10.3389/fphar.2014.00293
64. Kushida N, Fry CH. On the origin of spontaneous activity in the bladder. *BJU Int*. Jun 2016;117(6):982-92. doi:10.1111/bju.13240
65. Young JS, Matharu R, Carew MA, Fry CH. Inhibition of stretching-evoked ATP release from bladder mucosa by anticholinergic agents. *BJU Int*. Oct 2012;110(8 Pt B):E397-401. doi:10.1111/j.1464-410X.2012.10966.x
66. Christie S, Zagorodnyuk V. Time-of-day dependent changes in guinea pig bladder afferent mechano-sensitivity. *Sci Rep*. Sep 29 2021;11(1):19283. doi:10.1038/s41598-021-98831-x
67. Ihara T, Mitsui T, Nakamura Y, et al. The oscillation of intracellular Ca(2+) influx associated with the circadian expression of Piezo1 and TRPV4 in the bladder urothelium. *Sci Rep*. Apr 9 2018;8(1):5699. doi:10.1038/s41598-018-23115-w
68. Ihara T, Mitsui T, Nakamura Y, et al. The time-dependent variation of ATP release in mouse primary-cultured urothelial cells is regulated by the clock gene. *Neurourol Urodyn*. Nov 2018;37(8):2535-2543. doi:10.1002/nau.23793
69. Kimura Y, Honda M, Sasaki R, et al. The circadian rhythm of bladder clock genes in the spontaneously hypersensitive rat. *PLoS One*. 2019;14(7):e0220381. doi:10.1371/journal.pone.0220381
70. Iwamoto T, Torimoto K, Gotoh D, et al. Reduced salt intake partially restores the circadian rhythm of bladder clock genes in Dahl salt-sensitive rats. *Life Sci*. Oct 1 2022;306:120842. doi:10.1016/j.lfs.2022.120842
71. Thoma C. Urinary incontinence: The bladder sets its own clock. *Nat Rev Urol*. Oct 2014;11(10):544. doi:10.1038/nrurol.2014.248
72. Chihara I, Negoro H, Kono J, et al. Glucocorticoids coordinate the bladder peripheral clock and diurnal micturition pattern in mice. *Commun Biol*. Jan 21

2023;6(1):81. doi:10.1038/s42003-023-04464-3