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DISEASE MANAGEMENT

Take an individualised approach when treating frail, elderly patients with nocturia

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Abstract
Nocturia is a complex symptom that is attributed to a wide range of causes, including advanced age, comorbidities and medications. Non-pharmacological treatments are first-line options in the management of nocturia in frail, elderly patients due to their safety in this vulnerable population. If pharmacotherapy is required, the benefits must be carefully weighed against the potential for adverse effects. Desmopressin, α-antagonists, antimuscarinic drugs and β3-adrenergic agonists have been identified as potential pharmacological options, though the evidence for their use in frail, elderly patients is limited.

Nocturia is a complex symptom, with a multifactorial aetiology

Nocturia is defined as waking from sleep to void urine once or more at night [1–3]. Nocturia is categorised under the umbrella of lower urinary tract symptoms (LUTS); and further classified as a urine storage symptom, alongside urgency, frequency and urinary incontinence [2].

The are many potential causes of nocturia including:

- Advanced age may cause changes in bladder smooth muscle leading to reduced bladder capacity, bladder hypersensitivity due to changes in the central nervous system and dysregulation of arginine vasopressin (anti-diuretic hormone). Nocturnal polyuria due to increased nocturnal urine production, is a major causative factor of nocturia [1]
- Comorbidities such as diabetes mellitus, insomnia, renal failure, hypertension, benign prostatic hyperplasia (BPH) [1]. Additionally, overactive bladder (OAB) typically coincides with nocturia [3]
- Medications such as diuretics, calcium channel blockers, selective serotonin reuptake inhibitors (SSRIs) and lithium [1].

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Frailty in elderly patients complicates the management of nocturia [1], these patients are more vulnerable to stressors, have reduced physiological function and are more vulnerable to polypharmacy [1]. Although there is no formal definition for frailty [4], the Timed Up and Go Test may be a useful screening test [1, 4].

Nocturia should be managed in patients as it has a negative impact on quality of life (QoL), and it is a risk factor for falls, fractures and depression [1]. This article summarises treatment options for nocturia in frail, elderly patients as suggested by Wolff et al. [1].

Non-pharmacological treatments are first-line options

Non-pharmacological options are preferred for the management of nocturia in frail, elderly patients, due to safety concerns in this patient population. Additionally, many non-pharmacological options are cheap and simple to implement. Although direct evidence for their use in frail, elderly patients is limited, they are unlikely to cause harm [1].

Treatment options include:

- Managing oedema of the lower extremities with compressive leg stockings and/or elevating legs for 30–60 minutes in the evening [1]
- Managing fluid intake; either global restrictions in fluid intake to limit urine production to < 30 mL/kg every 24 h, or avoiding fluids 3–4 h prior to sleep [1]

- Pelvic floor exercises (Kegel exercises) to a total of 30 repetitions daily [2], or 45 repetitions daily for 3 days every week [1]
- Reducing salt intake in patients who are not at risk of orthostatic hypotension [1].

Optimise existing medications and be wary of polypharmacy

Polypharmacy is common in elderly patients as comorbidities are typically observed with advanced age [1]. Polypharmacy in frail patients is of concern as they are at greater risk of adverse outcomes. Although a causative relationship between frailty and polypharmacy is not conclusive, polypharmacy and frailty are intertwined. Frail patients are likely to require multiple drugs for treatment, which exposes them to a greater risk of adverse events that exacerbate their frailty. Furthermore, frail patients have altered pharmacokinetics, which may amplify drug-drug interactions and lead to toxicity [1].

Perform a medication review with the objective to eliminate or substitute drugs that are associated with nocturia, including diuretics, calcium channel blockers, SSRIs and lithium. Other suggested optimisation techniques include [1]:

- Administering diuretics in the afternoon and avoiding night time administration
- Optimising medications for diabetes mellitus to reduce polyuria
- Using continuous positive airway pressure for patients with obstructive sleep apnoea; disturbed sleep can lead to nocturia

The main objective of pharmacotherapy is to improve patients' quality of life

If non-pharmacological options have failed, pharmacological therapy should be considered after serious consideration of the benefits in QoL gains against the risk of adverse events [1]. Treatment should be individualised based on patients' risk factors and pill burden and treatment goals should be discussed with the patient and their caregivers. Close monitoring of patients after initiating pharmacotherapy for nocturia is recommended, and treatment should be discontinued if no benefits in QoL are observed [1].

Limited data are available for the safety and efficacy of pharmacotherapies in the management of nocturia and associated urological symptoms in elderly patients, as older patients are typically ineligible for enrolment in drug trials (Table 1). Scant data are available in frail patients, and it is unknown if the data in non-frail elderly patients are generalizable to frail patients [1].

Desmopressin is a useful pharmacological treatment, but be cautious of hyponatremia

Desmopressin is regarded as the first-line pharmacological treatment for nocturnal polyuria, though no specific studies have been conducted in frail elderly patients (Table 1) [1]. FDA contraindications for desmopressin therapy are CL_{CR} < 50 mL/min, hyponatremia or a history of hyponatremia [5]. However, the International Continence Society (ICS) does not recommend desmopressin in frail patients [4] and the AGS Beers Criteria lists desmopressin as a potentially inappropriate option in older adults [6]. Contraindications to the use of desmopressin, as defined by the ICS, are [1, 4]:

- Relative contraindications: frailty, sodium levels 130–135 mmol/L, uncontrolled hypertension or diabetes mellitus, concurrent use of angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, loop diuretics or antidepressants
- Absolute contraindications: sodium levels < 130 mmol/L, estimated glomerular filtration rate < 50–60 mL/min, New York Heart Association class II+ heart failure, polydipsia, obstructive sleep apnoea and severe leg oedema

Hyponatremia is a rare, but potentially fatal adverse event with desmopressin [5], and may contribute to an increased risk of falls in already frail patients [1]. The incidence of hyponatremia may be as high as 6% in patients aged > 65 years, with a higher incidence in women due to a higher sensitivity to desmopressin. Regular monitoring of sodium levels once every 6 months in patients aged > 65 years, including measurements at 3–7 days and at 1 month after initiating treatment (there is no specific guidance available for frail patients), is recommended [1]. Restricting or moderating fluid intake at or before bedtime is recommended by both the FDA and the ICS due to the increased risk of hyponatremia [4, 5]. Only the tablet formulation of desmopressin is approved in this indication; the FDA warns against the use of desmopressin nasal spray for the management of nocturia due to the higher risk of hyponatremia compared with the tablet formulation [5].

If desmopressin therapy is necessary, treatment should be initiated at the lowest therapeutic dose; patients should also be screened for hyponatremia and advised about the potential risks of desmopressin [1].

α-antagonists and antimuscarinic drugs may have limited use in frail elderly patients

Limited data for α-antagonists (including doxazosin, silodosin and tamsulosin), as well as the 5α-reductase

Table 1 Summary of pharmacological treatments for the management of nocturia in frail elderly patients, as suggested by Wolff et al. [1]

Drug	Formulations (FDA dosage [5])	Comments
Hormonal treatments		
Desmopressin	0.2 mg tablets (titrate to a max dose of 0.6 mg [5]); 0.83–1.66 µg/0.1 mL nasal spray; 25–50 µg sublingual wafers[a]	AVP analogue which exerts an antidiuretic effect by ↑ water resorption in the collecting duct and ascending loop of Henle [1]
		Significantly[b] ↓ mean nocturnal voiding frequency and ↑ hours of undisturbed sleep in a meta-analysis of 6 placebo-controlled trials [7]
		↓ nightly voids and nocturnal urine production, ↑ duration of undisturbed first period of sleep and QoL with desmopressin tablets vs placebo in a RCT of 115 men with BPH aged > 65 years [1]
		↓ nightly voids with desmopressin spray vs placebo in an RCT of pts aged > 50 years [8]
α-Antagonists		
Doxazosin and/or finasteride[c]	Doxazosin as 1–2 mg tablets (1 mg daily, max 8 mg daily); finasteride as 5 mg film coated tablets (5 mg daily)	Modestly[b] ↓ mean nocturia frequency with doxazosin ± finasteride (with no further benefit with combination therapy) vs placebo in a subgroup of pts aged ≥ 70 years after 4 years of treatment in an RCT of 2583 men with LUTS [9]
Silodosin or tamsulosin	Silodosin as 4–8 mg capsules (8 mg daily); tamsulosin as 0.4 mg capsules (0.4 mg daily, max 0.8 mg daily)	Modestly[b] ↓ nocturia frequency with silodosin vs placebo in pooled data from 3 RCTs with a total of 1479 men aged > 50 years [10]
		Significantly[b] ↓ nocturia frequency with silodosin (but not tamsulosin) vs placebo in an RCT of men with LUTS/BPH aged > 50 years [11]
		Significantly[b] ↓ the number of noctural voids, ↑ sleep scores and quality with tamsulosin in a prospective study of 296 women aged >20 years [12]
Antimuscarinics		
Fesoterodine	4–8 mg film coated, extended release tablets (4 mg daily, max 8 mg daily)	No significant change in the number of nocturnal voids in an RCT of 582 pts aged > 65 years [13]
β3-adrenergic agonists		
Mirabegron	25–50 mg film coated, extended release tablets (25 mg daily, max 50 mg daily)	Modestly[b] ↓ the number of nocturia episodes in one prospective trial of 217 patients aged ≥ 40 years [14]
		Modestly[b] ↓ the number of nocturia episodes in a meta-analysis of 10,248 pts with OAB from eight trials [15]

AVP arginine vasopressin (anti-diuretic hormone), *BPH* benign prostatic hyperplasia, *LUTS* lower urinary tract symptoms, *max* maximum, *OAB* overactive bladder, *pts* patients, *QoL* quality of life, *RCT* randomised control trials, ↑ increase(ing/ed), ↓ decrease(d)

[a]Unless stated otherwise, this is a summary of US, Australian and European prescribing information by the International Continence Society [4]. Consult local prescribing information for details

[b]Significant results are statistically and clinically significant; modest results are statistically significant, but are unlikely to be clinically significant

[c]5α-reductase inhibitor

inhibitor finasteride, suggest that they may be considered as a treatment option for the management of nocturia in elderly men, but not in elderly women as the only available data are from younger patients (Table 1) [1]. α-antagonists are typically used in the treatment of bladder outlet obstruction or BPH in men as they cause relaxation of the bladder neck or reduction of the outlet obstruction. The potential benefits of α-antagonists should be balanced against the increased risk of falls (as orthostatic hypotension is a notable adverse event of α-antagonists), especially in patients receiving concurrent treatment with nitrates. Although tamsulosin may have increased the risk of dementia in older men in one study, the evidence for a link between α-antagonists and dementia is unclear and further research is required to substantiate this relationship [1].

Recommendations for the use of antimuscarinic drugs, such as fesoterodine, vary for elderly patients [1–3]. Antimuscarinic drugs are typically used for the treatment of OAB in younger patients by inhibiting the micturition reflex to minimise detrusor contractions [1]. Limited data in frail patients aged > 65 years does not support their efficacy in the management of nocturia (Table 1) [1]. Furthermore, the AGS Beers Criteria classifies antimuscarinics used for urinary incontinence as a potentially inappropriate class of medications in older adults as their anticholinergic effects may exacerbate delirium or cognitive impairment [6]. There is some evidence for the use of

antimuscarinic drugs for the treatment of OAB in elderly patients (but not nocturia in isolation) [2, 3], and cognitive impairment due to anticholinergic effects was not observed in elderly patients during observational studies and randomised clinical trials [3]. However, the use of immediate release oxybutynin is not recommended due to the high incidence of adverse effects and potential for cognitive impairment at higher doses [2, 3].

β3-adrenergic agonists (e.g. mirabegron), are approved for the treatment of OAB, but they are not recommended in frail, elderly patients as they exhibited only modest improvements in nocturia for this patient population (Table 1) [1]. However, β3-adrenergic agonists may be an alternative for antimuscarinic drugs in the treatment of OAB in elderly patients, as they do not cross the blood brain barrier and lack antimuscarinic adverse effects [2].

Non-steroidal anti-inflammatory drugs (NSAIDs) have been investigated in the treatment of OAB, however, scant data are available for their use in the management of nocturia in elderly patients [1]. NSAIDs are not recommended for the management of nocturia in elderly patients [1]. The AGS Beers Criteria categorises the chronic use of NSAIDs in patients aged > 75 years as potentially inappropriate due to the increased risk of gastrointestinal bleeding [6].

Take home messages

- Use non-pharmacological options for the management of nocturia in frail, elderly patients due to their favourable safety profile.
- Review and optimise existing medications, including the elimination or substitution of drugs that cause or exacerbate nocturia.
- Balance any potential QoL benefits against the risks of treatment, if pharmacotherapy is required.
- Desmopressin and α-antagonists can play a role in the pharmacological management of nocturia or associated urological symptoms; limited evidence is available in frail, elderly patients.

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