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FEMALE UROLOGY (L COX, SECTION EDITOR)

Nocturnal Enuresis in the Adult

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Structured Abstract

Purpose of Review The goal of this paper is to describe the pathophysiology of adult nocturnal enuresis and develop a generalized approach for evaluation and treatment.

Recent Findings Although nocturnal enuresis (NE) impacts a significant proportion of the adult population, research on this topic remains lacking. In the few existing studies, the management strategy is extrapolated from research on pediatric nocturnal enuresis. Furthermore, treatment approaches highlight the importance of identifying risk factors and contributing pathologies. The modern urologist should understand the complexity of this problem and the variety of techniques to evaluate and treat the adult patient with NE.

Summary Adult nocturnal enuresis is multifactorial and may have multiple underlying pathologies. A comprehensive workup requires an understanding of the patient's history and symptomatology and the pathophysiologic processes that can occur. Treatment should first target identifiable etiologies, although a generalized algorithm can then be utilized with behavioral and lifestyle modifications, followed by medical therapy. Future studies will provide a better framework for treating this problem.

Keywords Nocturnal enuresis · Nocturnal polyuria · Nocturia · Desmopressin · Urinary incontinence

Introduction

Nocturnal enuresis (NE) is traditionally described as a urologic problem that affects the pediatric population. However, studies have shown that NE may actually affect 2–6% of adults [1, 2]. And while the diagnostic and management algorithm for pediatric NE is well established, guidelines for adult NE are profoundly incomplete.

The impetus to refine our approach to this problem centers on its impact on the patient's well-being. Adults with NE are more likely to suffer from depression and anxiety, although causality remains unclear. What is clear is that NE disrupts an individual's normal way of living. The sleep disturbances that result from NE may cause sleep deprivation, mood changes, lower self-esteem, and chronic fatigue. And as many as one third of these patients feel that it affects their job performance, employment, or social activities [2, 3•]. Furthermore, NE can be a safety concern, as it poses a risk for mechanical falls in the elderly [4]. Overall, NE is a life-altering condition and may be a cause of social and psychological distress to patients. And this is all complicated by the potential stigma attached to enuresis, which may prevent or delay the patient from seeking treatment.

Definition and Classification

Nocturnal enuresis is defined as involuntary voiding during night-time sleep [2, 5]. It can be classified based on its chronicity. Primary NE indicates that NE was present in childhood and either persisted or recurred in adulthood. Recurrent primary NE is present when the patient was dry for at least 6 months prior to the recurrence. For ease of management, both types of primary NE can be grouped into one diagnostic category.

Primary NE accounts for most cases of adult NE. And compared with childhood NE, primary NE tends to be more severe; the majority (79%) of adults with NE experience moderate or severe symptoms, with at least three episodes per week [2, 5]. As such, primary NE in adults is more difficult to treat and less likely to resolve spontaneously. In regard to

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other urinary symptoms, the association of primary NE with other lower urinary tract symptoms (LUTS) is quite variable. However, the absence of other voiding complaints does not necessarily indicate that there is healthy bladder function, as many of these patients may have urodynamic evidence of detrusor overactivity (DO), functional bladder outflow obstruction (BOO), or decreased bladder capacity [6].

The other classification, secondary adult onset NE, has no pediatric component and begins in adulthood. This is more common in females, whereas primary NE is more prevalent in males. Furthermore, secondary NE is often associated with LUTS and voiding dysfunction [1]. Adult onset NE without daytime incontinence is a rarity and affects only 0.02% of the population.

The other method of classifying adult NE is based on the presence or absence of associated LUTS. This system uses the terms monosymptomatic NE and polysymptomatic NE.

Anatomy and Physiology

The normal functional bladder capacity in adults is 300–400 mL [7, 8]. Several factors play into this, including adequate compliance, functional and closed urethral sphincters, and intact sensory, motor, and autonomic nervous innervation. Over the course of a night, as the bladder fills to its capacity, the bladder outlet and sphincter normally remain closed. When the bladder volume reaches its functional capacity, the individual is awakened and the patient can defer voiding without leakage until a bathroom is accessible [9••].

Another important factor that enables nocturnal continence is the diurnal variation in secretion of arginine vasopressin (AVP), which in its functional form is antidiuretic hormone (ADH). AVP is produced by the hypothalamus and stored in the posterior pituitary. It acts on the renal collecting system to facilitate the reabsorption of water. AVP is normally secreted in a diurnal pattern, resulting in the production of lower volumes of concentrated urine overnight [10]. This ensures that the nocturnal urine production does not exceed functional bladder capacity, and the individual can sleep through the night without needing to void. Disruption of normal nocturnal AVP levels leads to nocturnal polyuria (NP) and can be seen in the young, the elderly, and patients with spinal cord injury (SCI) [11]. Interestingly, there is a gender difference in causes of nocturia; NP predominates in men, whereas reduced nocturnal bladder capacity predominates in women [12].

One other important element in this discussion is the changes that occur in voiding function as an individual ages. This includes decreased bladder sensation, decreased detrusor contractility, decreased tone in the pelvic floor musculature, and increased residual volume [8]. There is also upregulation of purinergic receptors and increased acetylcholine release in the urothelium, both of which may contribute to the higher prevalence of overactive bladder (OAB) symptoms in adults. Despite all of these micro- and macroscopic changes, the development of life-altering bladder symptoms is not normal. The adult body should be able to accommodate all of these changes by altering bladder habits, ideally without a significant change in daily living.

Associated Conditions, Risk Factors, and Pathophysiology

There are many conditions and medications that are linked to adult NE. Neurologic diseases such as SCI may have a role in NE via several mechanisms, including nocturnal polyuria, overactive or underactive bladder, or sphincter incompetence. The overproduction of urine at night is of particular interest in this population, as it can be targeted with therapy. The International Continence Society (ICS) characterizes NP as night time urinary output in excess of 20% of the total 24-h output in the young and exceeding 33% in the elderly [9••, 12]. There are two main mechanisms to explain this in SCI patients. First, they may not have the normal diurnal variation in AVP levels. Second, there is disruption of the normal autonomic regulatory mechanisms that modify vascular tone and prevent postural fluid shifts. Consequently, body fluid pools in the lower extremities during the day, and then, excess fluid returns to circulation at night, resulting in diuresis [11]. In fact, congestive heart failure may cause nocturnal diuresis by a similar mechanism [13]. Correcting this aberrant physiologic pathway can thus improve NE in this patient cohort [11].

Sleep disorders are also linked to NE, most notably obstructive sleep apnea (OSA) [13, 14]. OSA disrupts the normal sleep cycle and results in periods of deep sleep with higher arousal threshold. In addition, elevated levels of atrial natriuretic peptide (ANP) are stimulated by the increased negative intrathoracic pressure [13]. This can create a nocturnal diuresis and overwhelm an individual's functional bladder capacity.

There are various other reported risk factors for NE, including smoking, obesity, hypertension, and a sedentary lifestyle [14, 15]. Many of these are associated with other urologic problems, so it is unclear if they play any direct role in NE. Patients with fluid overload states are at risk for NP and thus NE. These include congestive heart failure, liver disease, and venous stasis [12]. Renal diseases have also been linked to NE, including diabetes insipidus and chronic kidney disease [5, 13]. Finally, there is an interesting correlation of NE with hemoglobinopathies, particularly sickle cell disease and thalassemia major [16]. While various mechanisms have been suggested—nephropathy, psychological factors, and anemia—the exact pathophysiology remains uncertain.

Urinary Tract Dysfunction

At the center of the discussion on nocturnal enuresis is understanding the patient's voiding habits as a whole. The clinician

can first focus on the bladder's ability to function as a storage reservoir. Dysfunctional storage may play a central role in NE [3•, 5, 6, 17].The finding of other urinary complaints, particularly frequency, urgency and urge incontinence, is more common in individuals with NE. At least one third of these patients report non-NE urinary symptoms. More specifically, detrusor overactivity (DO) may play a role in both primary and secondary NE [2]. In 30 young adults who underwent UDS studies for primary NE, 93% were found to have DO. Moreover, adult women with overactive bladder (OAB) symptoms—urgency, frequency, and nocturia—are at increased risk for experiencing NE [3•, 18]. Thus, the joint entity of OAB and DO may explain the mechanism of NE in a notable subset of patients.

There is also evidence to suggest that impaired emptying and lower urinary tract obstruction contribute to NE. Men presenting with LUTS and secondary NE are often found to have anatomic bladder outlet obstruction (BOO). This may present with other LUTS, and treatment of the BOO has a high chance of resolving the NE [1]. Functional outflow obstruction may also be seen, although much more commonly in younger patients with primary NE. In young adults undergoing UDS for primary NE, nearly 75% had evidence of functional bladder outflow obstruction, including dysfunctional voiding and detrusor sphincter or detrusor pelvic discoordination [6]. This again supports the rationale for differentiating primary from secondary NE, as this designation can point to different etiologies and treatment strategies.

NE may also be a sign of urinary retention and overflow incontinence, with outflow obstruction or hypoactive bladder as the culprit [9••]. During the day, the individual may compensate for altered bladder function with timed voiding or double voiding. However, in a deep sleep, this is not possible, revealing urinary retention, overflow incontinence, and NE.

It is furthermore possible that bladder dynamics, including capacity and compliance, are at the center of certain cases of NE. A poorly compliant bladder with low capacity cannot accommodate nocturnal urine production. This may be seen in patients with neurological diseases, recurrent infections, scarring, or long-standing outflow obstruction [5]. One study demonstrated that half of young patients with primary NE had reduced capacity less than 300 mL on UDS [6]. Similarly, in men with secondary adult onset NE, a significant proportion may have diminished compliance [1].

Another vital component in urinary continence, whether during the day or at night, is a closed and functional urinary sphincter. Many variables affect this, among them pelvic and transurethral surgery, radiation, neurological processes, and the decreased sphincter tone that accompanies aging. Depending on the severity, intrinsic sphincter deficiency (ISD) and stress urinary incontinence (SUI) would likely result in both day and night incontinence. These are well-known risk factors for adult NE, particularly in females [18]. This reinforces the importance of assessing all of an individual's urinary complaints to determine the etiology of NE.

Interestingly, there is evidence that patients who have undergone cystectomy and creation of an orthotopic neobladder may present with NE as their chief complaint [5, 19]. Proposed mechanisms involve weakness of the urinary sphincter as well as nocturnal diuresis, which may relate to increased daytime fluid absorption from the neobladder. These patients are also at risk for impaired neobladder function and abnormal UDS profiles and tend to have higher residual volumes, raised neobladder pressures, and a lower urinary flow rate [19].

Medications

Medications play a role in NE by three main mechanisms—sedation, impaired bladder function, or diuresis. Sedatives affect NE by increasing the sleep arousal threshold and decreasing urinary sphincter tone. The most commonly reported sedating drugs including alcohol, benzodiazepines, non-benzodiazepine hypnotics such as zolpidem, and antihistamines [9••]. Antipsychotic medications such as quetiapine, olanzapine, and clozapine can also have a sedating effect, although they also act by impairing bladder emptying [5]. Alcohol is another well-known drug implicated in cases of NE, as it has both sedative and diuretic effects. Lastly, the diuretics commonly used for congestive heart failure and lower extremity edema can cause NE, especially if administered at bedtime.

Diagnosis and Evaluation (Table 1)

NE can present in many different forms and may be multifactorial in etiology. It is thus vital to employ a standardized approach when evaluating patients. The first step is a detailed history and physical exam. This should focus on associated LUTS, past medical and surgical history, and medications. It is important to differentiate true NE from nocturnal incontinence, which is characterized as waking due to urgency but not making it to the bathroom prior to voiding. Next, the patient should complete a frequency-volume diary, as this will elucidate fluid intake, daytime and nighttime symptoms, and frequency of episodes. It will further identify patients with nocturnal polyuria and the appropriate treatment strategy.

A comprehensive physical examination is also fundamental, with particular focus on the neurologic and genitourinary components. A digital rectal exam should be included in all males to assess the size of the prostate. The patient should submit a formal urinalysis to assess for other abnormalities and rule out a urinary tract infection. A post-void residual should be measured in all patients to assess for urinary retention, especially in male patients given the risk of BOO. In

Table 1 Diagnostic algorithm for adult NE

Patient group and indications	Evaluation	Goal/findings
All patients	History	LUTS, medical and surgical history, medications; differentiate NE from nocturnal incontinence
	Physical exam	Neurologic exam, DRE for prostate enlargement
	Frequency-volume diary	Fluid intake, nocturnal polyuria, daytime and nighttime symptoms, and frequency of episodes
	Post-void residual	Assess for urinary retention
	Urinalysis	Assess for urinary tract infection
Select patient with suspicion for BOO	Uroflowmetry	Assess for lower urinary tract obstruction and hypotonic bladder
Select patients with LUTS, other risk factors, or incomplete diagnoses	Urodynamics study	Assess for DO, reduced compliance/capacity, functional/anatomic obstruction
	Ultrasound Cystoscopy	Only if a concerning etiology is discovered that would otherwise warrant these tests

LUTS lower urinary tract symptoms, *NE* nocturnal enuresis, *DRE* digital rectal exam, *BOO* bladder outlet obstruction, *DO* detrusor overactivity

addition, uroflowmetry can be obtained in select patients with suspicion of lower urinary tract obstruction.

The next test in our algorithm is a urodynamic study. Before utilizing this test, which is costly and invasive, it is important to reassess the particular individual and his/her complaints. A young adult with primary persistent NE, a normal exam, and no evidence of bladder dysfunction, may potentially avoid UDS testing and proceed straight to treatment with desmopressin. Another example is an older male patient found to have an enlarged prostate, urinary retention, and overflow incontinence. This patient may not require UDS prior to treatment for BOO. However, it must be noted that a significant proportion of adults with NE will have abnormal UDS findings. Many young adults with primary NE have evidence of dysfunctional voiding and abnormal UDS evaluation [6]. Additionally, a significant proportion of older men and women with secondary NE will have abnormal UDS profiles even in the absence of other LUTS [1, 15]. Thus, the clinician must assess the potential benefits and harms of a UDS evaluation in each individual patient.

We recommend a UDS study in the patient with other urinary complaints or other abnormalities (prior urologic surgery/treatment or a neurologic condition), as this may expose an underlying pathology. Similarly, if an initial treatment is ineffective in a patient that is otherwise thought to be straightforward, a UDS study is appropriate.

Remaining tests such as ultrasound and cystoscopy are unnecessary in the majority of patients unless a concerning etiology is discovered that would otherwise warrant these tests.

Treatment

Treatment regimens should be tailored to the specifics of each case—age, sex, comorbidities, and the classification of NE (primary or secondary, monosymptomatic or polysymptomatic). Furthermore, therapy should target the etiology of NE, if it can be identified. And as NE is often multifactorial, it is often prudent to utilize a multidisciplinary team.

Here, we will provide a general treatment algorithm for the patient with NE.

First-Line Therapy

Regardless of the etiology of NE, the clinician should focus on behavioral and lifestyle changes as first-line therapy. Any offending medications or drugs should be modified or discontinued as much as the patient is able. This becomes more complex with medications such as antipsychotics or diuretics, which reinforces the importance of coordinating care with other disciplines. Healthy sleeping habits should be introduced; the patient should avoid sleep cycle altering drugs and night-time diuretics such as caffeine and alcohol [20•]. This is also a good opportunity for the clinician to address possible risk factors such as obesity and smoking. Weight loss in particular may help if OSA is a contributing factor.

Furthermore, the diagnosis of OSA should prompt referral to the primary care physician or an appropriate sleep specialist, as resolution of this problem may cure the patient's NE. Other medical problems such as depression and anxiety may also come to light during the evaluation for NE and would warrant treatment. The management of comorbid conditions such as neurologic disease can be complex as it involves multiple mechanisms. As such, medical therapy may be beneficial to this subset of patients, as outlined below. Finally, any infections should be treated with culture-directed antimicrobial therapy.

An important aspect of first-line therapy is behavioral modification. Treatment of pediatric NE supports the use of timed

voiding, pre-sleep voiding, and enuresis alarms [5]. The adult NE population may also benefit from timed voiding and double voiding prior to bedtime, as these have established success for managing such problems as nocturia, nocturnal polyuria, and OAB [20•]. As with any intervention, though, patients must be carefully selected, as elderly patients may not benefit as much. Timed voiding in particular has shown no efficacy in reducing NE in the elderly and furthermore negatively affects sleep cycles [21].

Given their success in pediatric NE, enuresis alarms would most likely benefit younger patients with primary NE. This is a relatively low risk intervention, but it requires a significant time commitment and compliance to a new schedule and regimen, which can limit its success in the adult population [5, 9••]. One extension of this is adapted clinical dry bed training (ACDBT). This is an intensive regimen of behavioral modification with enuresis alarms, which has shown efficacy in young adult women with mild NE [22].

On the contrary, modifying fluid intake is a more practical and less intensive change. In the pediatric population, guidelines recommend evaluating for excessive fluid consumption. Children with NE can be instructed to reduce fluid intake in the 1–2 h before bedtime as long as they compensate for this by increasing consumption earlier in the day [23]. The same principles can be applied to adults. This behavioral modification technique is utilized in the management of nocturia and OAB and may act similarly in NE by reducing nocturnal urine output [24, 25]. However, extra care must be taken in the elderly so as not to cause dehydration and electrolyte abnormalities. In addition, patients with excessive daily fluid intake should be counseled on normal levels of fluid consumption.

Second-Line Therapy

The next step in management of adult NE is to treat any identifiable disease process (Fig. 1). This includes nocturnal polyuria, OAB/DO or impaired bladder compliance/capacity, BOO, ISD or weak pelvic floor, hypotonic/insensate bladder, and orthotopic neobladder. The clinician should follow subspecialty guidelines on treatment approaches for these specific etiologies.

Third-Line Therapy

If a patient continues to experience NE despite treatment of identifiable disease processes or the patient has no identifiable pathology, then medication therapy for NE can be considered. Medication therapy for NE includes desmopressin and anticholinergics.

Desmopressin

Desmopressin is a synthetic analogue of the hormone AVP and, as such, acts as an antidiuretic agent by increasing water reabsorption in the kidney [10]. It can be used in patients with nocturnal polyuria refractory to first-line interventions, as well as patients with suspected abnormalities of AVP secretion (young patients with primary NE, elderly, SCI, OSA). For idiopathic NE, we recommend a starting dose of 0.1–0.2 mg, which can be titrated higher for efficacy. A greater dose may be required for OAB patients [26]. Both intranasal and oral formulations are effective. It is important to inform patients who achieve success about the need to continue the medication indefinitely, as the vast majority of patients relapse when the medication is stopped [26–28]. Furthermore, the patient should be counseled on potential adverse effects, most notably hyponatremia and fluid retention. This is more prevalent in elderly patients above 65 years of age but can usually be prevented with fluid restriction overnight [10]. Two strategies to minimize this complication include starting with a lower dose (0.1 mg) and periodically checking sodium levels [10, 29]. One recommendation, particularly in the elderly, is to check serum electrolytes at baseline, 3 days after starting therapy, 1 week later, and then at regular intervals in follow-up every 1–3 months.

For younger individuals with primary NE, desmopressin has approximately a 50% success rate [26–28]. Patients may be more likely to respond to desmopressin therapy if the nocturnal urine output exceeds functional bladder capacity [28]. There is at least a 75% recurrence rate when the medication is discontinued. In one study, enuresis alarms were utilized when patients relapsed, and this achieved a 33% cure rate without the need to restart desmopressin [27]. This reinforces the potential role for behavioral therapy in younger patients with primary NE, even in those who fail medical therapy.

Studies about desmopressin specifically for NE in an older adult population are lacking, although we can extrapolate its efficacy from its use in nocturia [10, 30, 31••]. Desmopressin can reduce the number of nocturnal voids and increase uninterrupted sleep time. It is generally well tolerated, and the majority of AEs are mild or moderate in severity, mostly including headache and dizziness. A small proportion of patients may develop hyponatremia, and age greater than 65 years indicates higher risk. For this reason, it may be prudent to start at a lower dose in the elderly with regular surveillance of serum sodium levels.

Low-dose desmopressin (0.1 mg) has also shown efficacy in patients with orthotopic neobladders, potentially helping as much as 50% of patients without any major adverse events or cases of hyponatremia [19, 32].

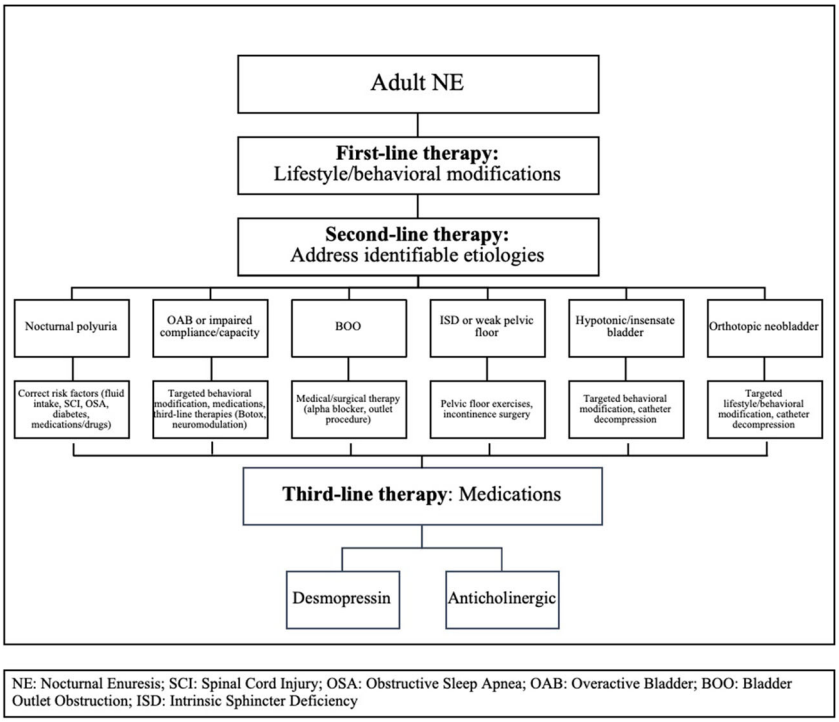

Fig. 1. Management strategy for adult NE

Anticholinergics

An anticholinergic can be added in desmopressin non-responders. It is approved for pediatric NE; thus, it may be most beneficial in younger patients with primary NE [33]. This approach can be utilized even in the absence of clear OAB symptomatology, although it would likely be more effective if there was clinical or urodynamic evidence of OAB/DO. Unfortunately, there is a dearth of evidence for anticholinergics in idiopathic NE. A small study of 20 young adults with primary NE showed that the addition of tolterodine achieved dryness in a small subset of patients that did not respond to desmopressin 0.4 mg alone [26]. Patients with orthotopic neobladders and NE may also benefit from anticholinergic therapy. In a group of 20 male enuretic patients with neobladders, anticholinergics improved NE and further showed urodynamic improvement in neobladder capacity and terminal DO, despite no change in compliance [19].

Patients with SCI and NE may benefit from a combination of an anticholinergic and desmopressin and has been effective in reducing reduce NE episodes, nocturnal urine production, and need for overnight CIC in this group [11, 34].

Before starting an anticholinergic, it is important to counsel patients on potential side effects including dry mouth and constipation. Elderly patients must be assessed for their risk of altered mental status. Patients should also be tested for incomplete emptying, as the antispasmodic effect of these drugs may lead to urinary retention, although this should be less likely in younger patients.

One final pharmacologic option is the tricyclic antidepressant, imipramine, which has been effective for severe refractory pediatric NE [27, 33]. It acts via several pathways, including its anticholinergic properties, reduced diuresis, and modification of the sleep and arousal mechanisms. As such, imipramine should not be used concomitantly with other anticholinergic medications. One study demonstrated an improved cure rate for young adults with NE when imipramine was added to desmopressin in desmopressin non-responders [27]. Imipramine may also improve NE in patients with nocturnal polyuria refractory to desmopressin [35]. When administering this medication, the clinician must consider potential cardiac side effects; imipramine should be used with caution in anyone of advanced age or with a cardiac history.

Surgical Therapy

There is no role for surgical intervention for idiopathic NE unless the evaluation has revealed targetable etiologies (see Fig. 1). Disease processes that receive well-established benefit from procedural intervention include OAB, BOO, and ISD, and treatment of these disease processes may improve NE symptoms. Specifically, neuromodulation with posterior tibial nerve stimulation or sacral nerve stimulation has been shown to improve bladder dynamics and decrease NE episodes and OAB symptoms [5]. A similar benefit is seen in patients with NE who are found to have BOO and subsequently undergo surgical resection of the obstructive tissue [1]. No studies have investigated incontinence surgery in this population.

Conclusions

Adult NE impacts a significant number of individuals, although a standardized approach to this complex problem remains absent. All patients should first be evaluated with a thorough history and physical exam, a frequency-volume diary, urinalysis, and measurement of post-void residual. A uroflowmetry can be performed in those patients in whom BOO is suspected. A UDS study can be avoided in straightforward cases with obvious etiologies but can be useful to expose underlying pathologies in the remainder of patients. After the workup is complete, treatment should first focus on behavioral and lifestyle modifications as well as targeting identifiable pathologies. For cases of refractory or idiopathic NE, pharmacologic therapy may be appropriate with desmopressin and anticholinergics. Specific disease processes such as SCI, OSA, and orthotopic neobladder may require a tailored treatment regimen. Finally, there is minimal role for surgical intervention for idiopathic adult NE.

Overall, adult NE poses a complex clinical entity with many potential factors and requires a comprehensive and multidisciplinary approach to best care for this patient. Future studies will provide a better framework for treating this problem.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent and Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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