A comprehensive review of adult enuresis

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Abstract
Nocturnal enuresis (NE) is a combined symptom of nocturia and urinary incontinence. In this review, we aim to summarize the current literature on NE in terms of its definition, diagnosis, and management. Recommended diagnostic evaluation of NE includes a focused history and physical examination, urinalysis, and when indicated, ultrasound examination, flow rate, urine volume chart, urodynamics, and cystoscopy. Therapeutic options include lifestyle modification and medications (i.e., desmopressin and anticholinergics).

Introduction
Gaining the ability to hold urine through the night is one of the developmental neuro-motor skills of a functioning bladder.1 NE is considered a physiologic finding in children less than five years of age, but is considered abnormal in adults. The International Continence Society (ICS) definition for nocturnal enuresis (NE) is any unintended voiding during night-time sleep.2 This definition lacks duration and frequency. In the current literature NE has been defined as one episode of nocturnal incontinence per 6 months or more,3 at least one time per week,4 or one per month.5

Regardless of underlying pathology, patients with NE experience discordance between bladder compliance, sphincter efficiency and urine production overnight and often lack of awareness of a sensation to void. Many adults afflicted with NE are affected psychologically. The aim of this article is to further understand the definition, diagnosis, and management of NE.

Classification
There are two types of adult enuresis classifications (Table 1).1,2,6-8 NE can be classified chronologically (i.e., primary versus secondary) or by symptomology (i.e., associated with LUTS or not).
Epidemiology

Prevalence
In adults the prevalence of NE has been reported as 2-3%. In females with voiding dysfunction and patients in nursing homes the prevalence is higher being 23% and 39%, respectively. In special populations, such as patients with Down syndrome, the prevalence is 17.2%.

Clinical course
The most common form of NE is persistent (PPNE; never dry for more than 6 months) following by recurrent (PRNE; dry for more than 6 months before adulthood recurrence) then secondary (SNE). In general, NE is associated with a higher number of episodes overall and is less likely to resolve if diagnosed as an adult compared to childhood diagnosis. It is unclear if progression of NE into the adulthood is dependent upon the severity of childhood presentation or if adult NE arises de novo due to different physiologic mechanisms.

Risk factors
Neurologic disease, psychiatric medications and sleep apnea syndrome are risk factors for NE. Smoking, obesity, decreased physical activity, and hypertension are risk factors specifically identified in women. In men benign prostatic hyperplasia and outlet obstruction are significantly associated with higher prevalence of secondary NE. Interestingly, NE in childhood does not increase enuresis risk in adulthood.

Psychosocial consideration
There is a significantly higher incidence of anxiety, depression, chronic fatigue and lower self-esteem in adults with NE as compared to the general population. Significant impact on psychosocial well-being has been noted in Western countries, Middle East countries, and Southeast countries. The relationship between psychological conditions and NE is complex. It is not fully established if these conditions result from NE or exacerbate NE.

Physiology
Pathophysiological mechanisms of nocturnal continence are outlined in Fig. 1. Briefly, through the night, a normal adult bladder can reach to volumes of 300 - 400 cc without needing to void due to bladder compliance and a closed outlet. Glomerular filtration typically decreases by 30% during the night and water reabsorption increases through the action of arginine-vasopressin. Thus, urine production decreases significantly. When one experiences increased volume of bladder to more than 300 - 400 cc a central mechanism awakens the person before unintentional voiding occurs.
Etiology
Etiologies of adult enuresis are classified as detrusor disorders, outlet issues, nocturnal diuresis and increased sleep arousal threshold (Table 2).

Multifactorial NE is common and can complicate clinical diagnosis. For example, diuretic use can increase nocturnal urine output and concurrent sedative use can increase sleep arousal threshold. Similarly, psychiatric medications such as olanzapine, clozapine and quetiapine,2,6 and risperidone21-23 can cause enuresis by several mechanisms including increased arousal threshold, increased urine production and decreased sphincter tone.6 Injured urinary sphincter during radical pelvic surgeries and concomitant polyuria caused by their continent pouch6 and abnormal bladder and sphincter function and nocturnal polyuria in spinal cord injury2,6 are other examples of multifactorial NE.

Assessment
Initial presentation of NE is typically managed by primary care physicians. Further work up by a urologist is advised for adults presenting with complex or prolonged bothersome NE.6 Suggested urologic evaluation is detailed in Table 3.

Details of assessment in adult enuresis is depicted in Fig. 2.

Management
Psychosocial stress, and bothersome NE episodes typically prompt treatment. First-line treatment options include lifestyle modifications, behavioral therapy and medical therapy. Other interventions such as surgical intervention, neuromodulation, Botulinum toxin injection to bladder have been used in some patients but are typically reserved as second-line modalities.

Lifestyle modification
Caffeine and sedative avoidance are suggested as they alter sleep cycle function. Alcohol avoidance is suggested due to its effect as a diuretic. Weight reduction can be advantageous through its effects of improving sleep apnea syndrome, and regular physical activity are potential ways to decrease the episodes of NE.13,18

Behavioural therapy
Although there is data to support time-voiding q2hrs and alarm system in children for NE26 there is no data in young adults. Furthermore, timed-voiding has a limited role in elderly patients with NE due to decreased adaptive conditioning skills and effect on sleep disturbances.13,26 Unfortunately, compliance with enuresis alarm systems is low in the adult population with a high withdrawal rate;4,6 however, when desmopressin failed to control enuresis, adding an alarm system has been reported to increase the response rate by 33%.2

Adapted Dry Behavioral Therapy (ADBT) is a cognitive behavioral and prompted voiding therapy which includes close observation during sleep, waking up frequently during night (every one hour), alarm use and day-time timed voiding. Although it is effective, high cost and time commitment deter its use commonly.24
Despite successful results in children, behavioral therapy is not as effective in adults. In selected adult cases (infrequent bed wetting, normal sonography and cystometric capacity greater than 300cc) it may have a contributive role.

**Specific treatments**
First-line therapy after lifestyle changes and behavioral therapy includes treating identifiable pathologies (Fig. 3). In addition to specific therapy any psychiatric contributors such as depression and anxiety should be addressed as well.

**Medical therapy**
In patients with NE with no defined etiology medical therapy is first-line. There are two classes of medications with supportive evidence: desmopressin and anticholinergics.

**Desmopressin**
Desmopressin has been accepted as first line therapy of idiopathic adult NE. Although some authors advocate to prescribe it only in the nocturnal polyuria variant of enuresis, currently it is the first treatment in adult NE with or without nocturnal polyuria.

Most patients require at least 0.2 to 0.4 mg of desmopressin per night; physicians should start at the low dose and titrate up. Patients with detrusor overactivity often require the higher dose (0.4 mg/day) to show any benefit. Once the suitable dose is found, decreasing or withdrawal of drug invariably causes symptom relapse and is therefore not recommended. Informing the patient about needing long-term therapy and the likelihood of decreasing the dose as well as safety of long-term usage of the drug helps should be highlighted during discussion before starting desmopressin.

Water intoxication and hyponatremia are dangerous and life-threatening complications. Fluid restriction from evening until morning is an efficient method to prevent these adverse effects. These complications are more common in the elderly. It is wise to check a serum sodium level at short intervals in first weeks of treatment.

**Anticholinergics**
In desmopressin non-responders, an anticholinergic medication can be added. In general there is good evidence for the safety of anticholinergics with urinary retention being a very rare side effect especially from younger population with NE. Imipramine as a peripheral anticholinergic and a drug with possible central effects have been shown to be effective in NE with polyuria. However, there are concern about its cardiac adverse effects in elderly patients. Watchful monitoring for urinary retention is important in patients utilizing anticholinergics.

Combination therapy is a long term and safe step in enuresis control. Discontinuation or decreasing dosage of drugs will often lead to symptom recurrence. If Desmopressin and an anticholinergic are not effective, Imipramine 25 to 50 mg per day has demonstrated benefit, but is uncommonly prescribed by urologists due to need for ongoing close follow-up and poor compliance due to sexual side-effects.
The flow of treatment steps for idiopathic nocturnal enuresis is outlined in Fig.4.

Other treatments
Minimal data exists to support surgical intervention for mono-symptomatic NE.\textsuperscript{12} Neuromodulation (peripheral and sacral) and botulinum toxin injection are capable of decreasing NE in patients with non-mono-symptomatic NE, however, there is no data supporting mono-symptomatic NE.\textsuperscript{2}

One randomized clinical study with 14 patients with refractory mono-symptomatic NE and abnormal detrusor function (over activity and reduced compliance) in each group has reported significant improvement in posterior tibial nerve stimulation arm in comparison to placebo.\textsuperscript{29}

Conclusion
Nocturnal enuresis is a symptom of urinary tract disorder or systemic disease. It requires a standard evaluation consisting of history and physical exam, urinalysis and when indicated urinary ultrasonography, Urine flow rate, frequency volume chart, urodynamic study and cystoscopy. It is recommended that general practitioners refer adults with NE to the urologist for this work-up because of its complexity.

There is minimal role for surgical intervention for this disease, except in specific populations. However, many patients benefit from long term Desmopressin. Anticholinergics can add benefit even in the absence of OAB symptoms. The role of neuromodulation, onabotulinumtoxin A and surgery are undefined in the literature. Behavioral techniques offer low risk intervention but their time commitment is considerable and they require a high degree of commitment on behalf of the patient to ensure compliance. Future studies should address these shortfalls in the literature to better manage adult patients with NE.
References

5. Yucel S, Ktlu O, Kukul E and Baykara M. IMPACT OF URODYNAMICS IN TREATMENT OF PRIMARY NOCTURNAL ENURESIS PERSISTING INTO ADULTHOOD. UROLOGY. 2004; 64 (5).


Figures and Tables

**Fig. 1.** Mechanisms of nocturnal continence.

![Mechanisms of nocturnal continence](image)

**Fig. 2.** Assessment in adult enuresis. UDS: urodynamic study.

![Assessment in adult enuresis](image)
**Fig. 3.** Specific therapy for adult enuresis. *Possible explanation for decreasing NE after mid-urethral sling placement is prevention of urinary leakage to proximal urethra and stress induced over-activity.**^{12} **^Higher severity of enuresis in hemolytic disorders is associated with increased admission; therefore, efforts to manage chronic disease may help manage and better treat NE. #Although in nocturnal diuresis due to overproduction desmopressin is treatment of choice one should be cautioned in patients with kidney and liver disease water intoxication and hyponatremia these should also be individually addressed. Multifactorial NE is difficult to treat and best controlled by multimodal approaches and addressing all contributing etiologies.**^{2,6} **For example, empirically patients with spinal cord injury and neo-bladder after radical pelvic surgeries are managed by low-dose desmopressin, oxybutynin 5 mg three times a day and catheterization before sleep.**^{2}
**Fig. 4.** Treatment steps for idiopathic nocturnal enuresis.

- **First step:** Life style modification and behavioural therapy
- **Second step:** Specific treatments
- **Third step:** Desmopressin
- **Fourth step:** Desmopressin & Anticholinergic
- **Fifth step:** Longterm Imipramine 25-50 mg/day
**Table 1. Adult enuresis classification**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Primary NE (PNE) (positive history in childhood)</th>
<th>Secondary nocturnal enuresis (SNE) (no evidence of NE in childhood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronologic classification</td>
<td>Persistent (PPNE) (never dry for more than six months)</td>
<td>Recurrent (PRNE) (dry for more than six months before adulthood recurrence)</td>
</tr>
<tr>
<td>Symptomatic classification</td>
<td>Monosymptomatic NE (the only symptom is NE)</td>
<td>Polysymptomatic NE (NE with other LUTS)</td>
</tr>
</tbody>
</table>

LUTS: lower urinary tract symptoms; NE: nocturnal enuresis.

**Table 2. Etiologies of adult enuresis**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Subtype</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrusor disorder</td>
<td>Detrusor over activity(^{12})</td>
<td>Neurogenic bladder</td>
</tr>
<tr>
<td></td>
<td>Detrusor hypo-compliance(^{12})</td>
<td>Idiopathic detrusor overactivity(^{1,6})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scarred bladder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic infection(^{1,6})</td>
</tr>
<tr>
<td>Outlet issues</td>
<td>Outlet obstruction(^{12})</td>
<td>Neurogenic bladder, BPH, urethral stricture</td>
</tr>
<tr>
<td></td>
<td>Outlet incompetence(^{12})</td>
<td>Neurogenic bladder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iatrogenic sphincter apparatus injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Nocturnal diuresis</td>
<td>Renal disorder(^{12,20})</td>
<td>Chronic renal disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal medullary concentration disorder (hemolytic disorders)(^{4})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diuretics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nephrogenic diabetes insipidus</td>
</tr>
<tr>
<td></td>
<td>Central disorder</td>
<td>Obstructive sleep apnea syndrome(^{2,6})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic liver disease(^{12,20})</td>
</tr>
</tbody>
</table>
Obstructive sleep apnea (OSA) syndrome increases secretion of atrio-natriuretic peptide during sleep and this results in nocturnal polyuria.\textsuperscript{2,6} BPH: benign prostatic hyperplasia.

Table 3. Adult enuresis assessment

<table>
<thead>
<tr>
<th>Type of assessments</th>
<th>Indication</th>
<th>Assessment</th>
<th>Details and findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential assessment</td>
<td>In all patients</td>
<td>History</td>
<td>Lower urinary tract symptoms, past medical and surgical history and medications\textsuperscript{1}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical examination</td>
<td>Focused neurological examination, digital rectal examination and bulbocavernous reflex\textsuperscript{1}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinalysis</td>
<td>To rule out urinary tract infection\textsuperscript{1}</td>
</tr>
<tr>
<td>Optional assessment</td>
<td>In patients with inadequate results with essential assessments</td>
<td>Urine flow rate (uroflow)</td>
<td>To screen silent obstruction or hypocontractile bladder\textsuperscript{2}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasound of upper and lower urinary tract and post voiding residue</td>
<td>To evaluate upper tract damages and lower tract efficiency in urine elimination\textsuperscript{2}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urodynamic study</td>
<td>Findings in SNE detrusor over activity, hypo-compliant bladder and silent bladder outlet obstruction\textsuperscript{2}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urodynamic studies have less value in PNE\textsuperscript{6,11}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cystoscopy</td>
<td>In cases with bladder outlet obstruction, posterior urethral valve and urethral stricture have been the most common findings (6.7%)\textsuperscript{11}</td>
</tr>
</tbody>
</table>

PNE: primary nocturnal enuresis; SNE: secondary nocturnal enuresis.