Vasopressin/desmopressin in the treatment of nocturia:

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Definition of nocturia

Nocturia defined by International Continence Society (ICS) as:

"the complaint that the individual has to wake at night one or more times to void ... each void is preceded and followed by sleep"

Van Kerrebroeck et al. 2002
What causes nocturia?

- Psychological/ sleep problems
- Primary polydipsia
- Oestrogen deficiency
- Untreated diabetes mellitus or insipidus
- Uncompensated heart disease
- Reduced bladder capacity
- Detrusor overactivity
- BPO
- Nocturnal polyuria

Fonda. BJU Int 1999;84(Suppl 1):13–15
Wein et al. BJU Int 2002;90(Suppl 3):28–31
Diagnosis of nocturia: urological causes

[Diagram showing the diagnosis process]

- Patient desires treatment
- Patient does not desire treatment

Screen

- Lifestyle advice

Further investigation

- Polyuria
- Nocturnal polyuria
- Mixed aetiology
- Apparent bladder storage problems
  - BPO
  - OAB

Nocturnal polyuria

Nocturnal polyuria (NP) is a major cause of nocturia

Defined as production of an abnormally large volume of urine during sleep:

- Output of >20% of daily total in young
- >33% in elderly
- Middle age between these extremes

Overactive bladder diagnosis does not exclude nocturnal polyuria

In EPIC\textsuperscript{1}, 12.8\% of women responders had OAB
Amongst women with OAB, 74\% had nocturia \textsuperscript{2}

Overall, 62\% of patients with OAB + nocturia (male and female) have nocturnal polyuria (NP)\textsuperscript{3}

Rate of NP in women with OAB + nocturia increases with age
Prevalence aged 65–74=0.86 [95\% CI: 0.62–1.00] \textsuperscript{4}

Nocturnal polyuria is inadequately treated in OAB patients on solifenacin monotherapy

Mean actual change in number of nocturia episodes from baseline

Without nocturnal polyuria

With nocturnal polyuria

n = 230 122 250 386 211 400

-0.1 -0.2 -0.3 -0.4 -0.5 -0.6 -0.7 -0.8

* p=0.026 vs placebo
** p=0.006 vs placebo
† p=non-significant vs placebo

Placebo
Solifenacin 5 mg
Solifenacin 10 mg

Nocturnal polyuria: therapy

- **Water diuresis**
  - Excessive evening intake → reduce
  - Abnormal vasopressin secretion → desmopressin
  - Idiopathic → combination (?)

- **Solute/water diuresis**
  - Congestive heart failure → legs up/stockings/CV ®/diuretics
  - Venous insufficiency → legs up/stockings/diuretics
  - Sleep apnoea → CPAP
  - Renal insufficiency → combination

Rationale for desmopressin use in nocturia

- Overall, 76% of individuals with nocturia have NP\(^1\)
- Of women with OAB and nocturia, 62% have NP\(^2\)
- Nocturia in OAB patients frequently not resolved using OAB therapies alone
- NP must be addressed specifically in order to achieve clinically significant improvement
- Desmopressin: antidiuretic agent capable of effectively reducing night-time urinary output

Vasopressin & Desmopressin

\[
\begin{align*}
\text{Vasopressin} & : \quad \text{H}_2\text{N-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH}_2 \\
\text{Desmopressin} & : \quad \text{deamino-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-NH}_2
\end{align*}
\]
Mechanism of Action (MOA)

- Antidiuretic effects mediated by stimulation of vasopressin2 (V2) receptors, increasing water re-absorption in the kidneys.

- Tubular re-absorption of filtered water → reduced urine production and bladder filling, delaying urge to void.
Desmopressin for nocturnal polyuria

Antidiuretic hormone/vasopressin (AVP) important for urinary concentration

- Increased plasma osmolality increases AVP release
- AVP increases water reabsorption in collecting duct of kidney via V$_2$ receptor

Proven benefit in polyuric conditions; ie nocturia, pituitary diabetes insipidus, PNE
## Desmopressin formulations for nocturia

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Composition</th>
<th>Indications</th>
<th>Dosage (adults with nocturia)</th>
<th>Key features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral tablet</td>
<td>Desmopressin acetate 0.1 mg and 0.2 mg</td>
<td>Nocturia, diabetes insipidus, nocturnal enuresis</td>
<td>0.1 mg at bedtime. Weekly dose escalations to a maximum of 0.4 mg if necessary</td>
<td></td>
</tr>
</tbody>
</table>
| Oral lyophilisate (Melt) | Desmopressin acetate 60 µg, 120 µg and 240 µg | Nocturia, diabetes insipidus, nocturnal enuresis | 60 µg sublingually at bedtime. Weekly dose escalations to a maximum of 240 µg if necessary | • Fast-melting  
• Dissolves instantly in the mouth – no need for water  
• Low dosing due to higher bioavailability¹ |

¹. Østerberg O et al. *Arch Dis Child* 2006;9:A31–34
Desmopressin: evidence for use in nocturia

- **Phase I:** initial studies in 24 nocturia patients
- **Phase II:** 2 controlled studies in 103 nocturia patients
- **Phase III: NOCTUPUS programme**
  - 3 short-term, multicentre studies
    - Double-blind, placebo-controlled, n=421
  - 2 long-term, open-label, extension studies
    - Up to 12 months, n=249
Desmopressin: Treatment for nocturia

- Fast onset of action
- Urine production decreases within 30 minutes of oral administration
- Available as oral tablet or lyophilisate formulation
- Not indicated for patients ≥65 years of age
- Level of Evidence 1, Grade A recommendation since 2004 for the treatment of nocturia of polyuric origin (ICI)
Primary endpoint: short-term studies

Proportion with ≥ 50% reduction in nightly voids

* $p < 0.0001$ (vs placebo)

Percentage of patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients with ≥ 50% reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>34%*</td>
</tr>
<tr>
<td>Female</td>
<td>46%*</td>
</tr>
<tr>
<td>Male / female</td>
<td>33%**</td>
</tr>
</tbody>
</table>

* $p < 0.0014$ (vs placebo)

Mattiasson 2002; Lose 2001; van Kerrebroeck 2002
Long-term studies: night-time voids

Mean reduction in night-time voids: men = 48–58%; women = 55–59%

Minimum serum sodium during treatment as a function of age

Min serum sodium during titration versus age – safety population

Min serum sodium during titration (mmol/L) vs. Age (years)

Non-hyponatr. male
Non-hyponatr. female
Hyponatr. male
Hyponatr. female

MIN/OCT/22FEB01/NaPlots.sas
Nocturia in men traditionally regarded as due to detrusor overactivity or bladder outlet obstruction (BOO) – caused by BPO. However, ~83% of male nocturia patients have nocturnal polyuria (NP).

<table>
<thead>
<tr>
<th>Causes of male nocturia (total n=41)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single isolated causes</strong></td>
<td></td>
</tr>
<tr>
<td>NP</td>
<td>8 (19.51)</td>
</tr>
<tr>
<td>Small nocturnal bladder capacity</td>
<td>2 (4.88)</td>
</tr>
<tr>
<td>BOO</td>
<td>1 (2.44)</td>
</tr>
<tr>
<td>Sleep apnoea syndrome</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Double combinations</strong></td>
<td></td>
</tr>
<tr>
<td>NP + small nocturnal bladder capacity</td>
<td>6 (14.63)</td>
</tr>
<tr>
<td>NP + BOO</td>
<td>8 (19.51)</td>
</tr>
<tr>
<td>Small nocturnal bladder capacity + BOO</td>
<td>4 (9.76)</td>
</tr>
<tr>
<td><strong>Triple combinations</strong></td>
<td></td>
</tr>
<tr>
<td>NP + small nocturnal bladder capacity + BOO</td>
<td>10 (24.39)</td>
</tr>
<tr>
<td>NP + small nocturnal bladder capacity + sleep apnoea syndrome</td>
<td>2 (4.88)</td>
</tr>
</tbody>
</table>

Chang et al. *J Urol* 2006;67:541–544
Are classical BPO treatments good enough?

- Various methods of treating BPO – based on assumption that all symptoms caused by prostate problems
  - α-adrenoceptor antagonists
  - 5α-reductase inhibitors
  - TURP
  - Phytotherapy
  - Combination therapy

- These can be effective for some LUTS, but nocturia – rated the most bothersome of LUTS – may not be significantly improved\(^1\)

TURP, transurethral resection of the prostate; LUTS, lower urinary tract symptoms

118/138 (85.5%) BPO patients had nocturia before TURP.

After treatment, 91 of these (77.1%) still reported nocturia.

Improvement in nocturia score (1.0) significantly inferior to improvements for all other IPSS symptoms.

<table>
<thead>
<tr>
<th></th>
<th>Patients scoring ≥2 score before TURP</th>
<th>Patients scoring ≥2 score after TURP</th>
<th>Rate of response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emptying</td>
<td>102</td>
<td>27</td>
<td>54.3</td>
</tr>
<tr>
<td>Voiding frequency</td>
<td>116</td>
<td>63</td>
<td>38.4</td>
</tr>
<tr>
<td>Intermittency</td>
<td>101</td>
<td>33</td>
<td>49.3</td>
</tr>
<tr>
<td>Urgency</td>
<td>103</td>
<td>70</td>
<td>37.0</td>
</tr>
<tr>
<td>Weak stream</td>
<td>122</td>
<td>35</td>
<td>63.0</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>84</td>
<td>18</td>
<td>47.8</td>
</tr>
<tr>
<td>Nocturia</td>
<td>118</td>
<td>91</td>
<td>19.6</td>
</tr>
</tbody>
</table>

TURP not the answer – are other mechanisms involved?

IPSS, international prostate symptom score

Yoshimura et al. Urology 2003;614:786–790
Tamsulosin OCAS not significantly better than placebo in reducing nocturnal voids

- 8-week study, n=117
- Some improvements in overall IPSS scores BUT
  - Mean reduction in number of nocturnal voids not significantly greater with tamsulosin OCAS than placebo (p=0.10)
  - Increase in duration of undisturbed sleep not significantly greater with tamsulosin OCAS than placebo (p=0.20)

OCAS, oral-controlled absorption system

NP often underlies failure of $\alpha_1$-blocker treatment for nocturia

Of 41 patients with nocturia which was not responsive to $\alpha_1$-blocker treatment, 85.4% found to have nocturnal polyuria.

Treatment specifically for nocturnal polyuria may improve nocturia.

Yoong et al. Med J Malaysia 2005;60;294–296
Up to 95% of BPE patients have NP and nocturia resistant to $\alpha_1$-blocker therapy

- 55/58 patients (95%) with LUTS suggestive of BPE found to have NP
- Of these, 20 received $\alpha_1$-blocker therapy for 6 weeks
  - NP unchanged in 75%
  - No significant difference in mean nocturnal urine production before and during therapy

BPE, benign prostatic enlargement; NP, nocturnal polyuria

Both genders benefit from desmopressin treatment for nocturia

*Clinical response defined as ≥ 50% reduction in mean number of nocturnal voids

Quality of sleep improves with treatment

“During the last week, did you often feel fresh in the mornings when you got up?”

- Desmopressin patients significantly more likely to show improvement vs placebo (26.6% vs 13.6% improved, p=0.02)

“During the last week, did you often feel tired during the day?”

- Improvement reported by 21.6% receiving desmopressin vs 12.1% with placebo (p=0.14)

OR, odds ratio; CI, confidence interval

How to treat nocturia of mixed aetiology

Adapted from van Kerrebroeck et al. *Neurourol Urodyn* 2002;21:179–183

OAB, overactive bladder

Patient desires treatment

Patient does not desire treatment

Screen

Lifestyle advice

Further investigation

Polyuria

Nocturnal polyuria

Mixed aetiology

Apparent bladder storage problems

BPO

OAB

---

OAB, overactive bladder

Adapted from van Kerrebroeck et al. *Neurourol Urodyn* 2002;21:179–183
If patients have >1 factor underlying nocturia, all these factors must be treated.

Nocturia in men with OAB and BPO does not respond adequately to monotherapy.

Combined tolterodine ER and tamsulosin therapy significantly better than placebo (p<0.05), and better than monotherapy.

- Improvement in nocturia not large, even with combined therapy (difference in reduction in micturitions/night vs placebo = 0.2)

N at baseline
Placebo: 215
Tolterodine ER: 210
Tamsulosin: 209
Tolterodine ER + tamsulosin: 217

Kaplan et al. JAMA 2006;296:2319–2328
Combination therapy may also be used for patients with nocturnal polyuria

Combination therapy should also take NP into account to alleviate nocturia

Patients may have:
- BPO + NP
- OAB + NP
- BPO + OAB + NP

Therefore:
- antimuscarinic + \(\alpha_1\)-blocker + desmopressin

may be required for successful nocturia treatment

Clinical studies to evaluate benefits of combination therapy are warranted

NP, nocturnal polyuria; BPO, benign prostatic obstruction; OAB, overactive bladder
Nocturia needs to be treated according to its causes

- If a patient has nocturia and diagnosis of OAB or BPO, they may ALSO have NP
- If NP present, consider combination therapy:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Desmopressin</th>
<th>Anticholinergic</th>
<th>α₁-blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAB</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>BPO</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>NP + OAB</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>NP + BPO</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>OAB + BPO</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>NP + OAB + BPO</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

Think beyond the bladder – to the kidneys!

- >80% of individuals with nocturia have NP
- NP comorbid with BPO and/or OAB must be addressed
- Desmopressin successfully treats nocturia caused by NP
- Combination therapy is a new emerging approach
- Desmopressin can be combined with anticholinergics + α₁-blockers to improve nocturia in patients with BPO and/or OAB with NP