Treatment of Nocturnal Enuresis

Dr. Anne Wright
Cape Town 2012
WAKES

YES

NO

FULL
BLADDER

NOCTURNAL
POLYURIA

SMALL
BLADDER

NOCTURNAL
POLYURIA

SMALL
BLADDER

WAKES

NOCTURIA

ENURESIS

After Hjalmas K. J Urol 2004
How many children can we help?

- The alarm (cure) Ia
- Desmopressin (treatment success) Ia
- Refractory nocturnal enuresis

All enuretic children
Meta-analysis of interventions for enuresis:

- Intervention versus no treatment
- for full response in children with bedwetting
- Relative risk > 1 favours the intervention
- If the 95% CI crosses 1 then the RR is not considered significant.

- Alarm + desmo gives the most
- Favourable RR 8.5

- NICE CG111, 2010
Correct understanding and use of the alarm
An operant conditioner

Only does two things:

• Teaches me to wake at time I need to pee
• Teaches me to get up and go to the toilet

Frustrations:

• I have to wet for it to work
• I have to get up and go to the toilet
• It takes a long time for things to get better
Predictive factors for Success

- Good motivation
- Tolerant parents
- Supportive family
- No multiple overnight bedwetting
- No daytime wetting
Correct understanding and use of the alarm
Combination with desmopressin

Are the following present?

- Partial response to the alarm
  - Some signs of waking
  - Some reduction in amount of wetting
- Willingness to continue with alarm

Step 2: Alarm + Desmopressin

- Combination of A+D is effective
  - Sukhai RN et al Eur J Pediatr 1989
  - Bradbury MG et al Acta Paediatr 1995
  - Vogt M et al BJU Int 2009
  - Gibb S et al J Pediatr 2004
  - Ng C F et al Pediatr Nephrol 2005

- **NICE** health economic analysis
  - *Probability that the strategy is most cost effective (threshold £20000/QALY)*  15.9%
    - NICE Nocturnal Enuresis guideline 2010
Correct understanding and use of desmopressin; an analogue of vasopressin.

Timing and dose

- Treatment group

- Placebo
- Desmopressin (30 μg)
- Desmopressin (60 μg)
- Desmopressin (120 μg)
- Desmopressin (240 μg)
- Desmopressin (360 μg)
- Desmopressin (300 μg)
- Desmopressin (480 μg)

Osmolality (mOsm/kg) vs. Time from dosing (hours)

Vande Walle et al. BJU Int 2006;97(3):603–9
Safe use of desmopressin

- Fluid restriction before bed
  - Sporting activity at night
- Caution coexistent conditions
  - Cystic fibrosis
  - D&V
  - ADHD
  - Prader Willi
- Supervision of younger children
- Caution with prodromal symptoms; headache, nausea, vomiting

  - Thumfart J Urol 2005
Using Desmopressin

- Desmopressin can be used for as long as symptoms persist
  - reassess every 3 months (minimum one week off treatment)

- Desmopressin does not suppress endogenous vasopressin after 24/52 tmt

Knudsen UB Urol Res 1991

<table>
<thead>
<tr>
<th>DesmoMelt</th>
<th>1 x 120 mcg Melt at bedtime, increasing to 2 only if necessary</th>
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<tbody>
<tr>
<td>Desmotabs</td>
<td>0.2 mg desmopressin tablets</td>
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Clinically sig hyponatraemia; desmopressin

- Intranasal preparation
  - 172 reports
    - 145 PMS
    - 27 additional Medline
- Pharmacokinetics
  - 6-24 hours (prolonged effect in some children)
    Dehoorne J Urol 2006

- Oral preparation
  - 6 reports
  - Duration of action is dose dependent with optimal dose giving 6-8 hours duration
    Robson J Urol 2007
Reduced nocturnal bladder capacity: mono- and non-monosymptomatic enuresis

• Small bladder (monosymptomatic)
  • Alarm treatment increases bladder capacity in children with MS non-polyuric NE
    • Taneli C; Scand J Urol Nephrol 2004
    • Hvistendahl G; J Urol 2004

• Overactive bladder (OAB/non-monosymptomatic)
  • Daytime LUT symptoms in addition to enuresis
  • Nocturnal OAB
Small capacity bladder: monosymptomatic and non-monosymptomatic

Evidence of small BC
- Not revealed in history
- Poor fluid intake by day
- Forgot to ask about when he was younger
- Nocturnal DOA only  Yeung CK J Urol 1999

Bladder diary
- Two spontaneous days
- Two days with recommended fluid intake

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Total drinks per day</th>
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<tbody>
<tr>
<td>4 – 8 years</td>
<td>Female, Male</td>
<td>1000 – 1400 ml, 1000 – 1400 ml</td>
</tr>
<tr>
<td>9 – 13 years</td>
<td>Female, Male</td>
<td>1200 – 2100 ml, 1400 – 2300 ml</td>
</tr>
<tr>
<td>14 – 18 years</td>
<td>Female, Male</td>
<td>1200 – 2500 ml, 2100 – 3200 ml</td>
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Anticholinergic + desmopressin
- **It makes sense**
  - Less urine (D)
  - Larger container (AC)
    - Austin PF et al Pediatr 2008
    - Neveus T et al J Urol 2001
    - Radvanska V et al J Urol 2006
    - Lee T et al J Urol 2005
    - NICE Health economic probability 19.8% 2010

- Tolterodine
  - 2mg at bedtime only

- Oxybutynin
  - 5mg at bedtime only

- Night-time only dose
  - Less side effects by day
  - Less worry about PVR

- Long acting AC
  - Steady state
  - Use of newer more bladder-selective ACs with less adverse effects e.g. Tolterodine XL/solifenacin
Third-line medication

Imipramine

- Grade Ia evidence of efficacy
  - Older studies
  - Neveus T et al Pediatr Nephrol 2008
- Good efficacy but less effective than first line
- But more adverse effects
  - Cardiotoxic (hypotensive/arrhythmias assoc with prolonged QT)
  - Needs adult supervision and safe storage
  - Also minor side effects
    - GI, anticholinergic, mood
  - Combine with desmopressin if partial response

- Appears to be useful in children with ADHD
  - Up to 32% of children with ADHD have enuresis
  - 30-40% of children with enuresis have ADHD
  - Higher association with inattentive subtype
  - Treatment failures assoc with poor compliance and IQ
  - Atomoxetine useful for enuresis in ADHD

Elia J J Pediatr 2009
Crimmins C R J Urol 2003
Sumner CR J Child Adolesc Psychopharmacol 2006
Complementary therapies

Cochrane review: Complementary and miscellaneous interventions for nocturnal enuresis in children  Huang T Dec 2011

“There is weak evidence to support the use of hypnosis, psychotherapy, acupuncture, chiropractic and medicinal herbs but it was provided in each case by single small trials, some of dubious methodological rigour”
What did I miss?

- Obstructive sleep apnoea
  - Basha S Laryngoscope 2005
  - Weissbach A Int J Pediatr Otorhinolaryngol
  - Kovacevic L J Ped Urol epub 2012

- Psychosocial issues

- Significant bladder dysfunction
  - 65% of children with refractory MNE have daytime bladder dysfunction
  - Older boys have cystoscopic obstructive features
  - Yeung CK J Urol 1999

- Constipation
What did I miss the first time round?

- Time to be a young scientist
- Hospital homework
- Revisit monitoring of
  - Bladder capacity
  - Nocturnal urine production
  - Patterns of fluid intake
  - Bowel function
- *Urinary tract ultrasound +/- uroflow/EMG + PVR
Suggested protocol

First try
Proper evaluation, proper bladder advice and desmopressin or the alarm

Second try
The alarm or desmopressin or alarm+desmopressin

Third try
Anticholinergics + desmopressin or Imipramine +/- desmopressin

Extended evaluation (voiding charts, flowmetry etc)
Exclusion/treatment of complicating bowel/bladder factors
How many can we help?

The alarm (cure)

Desmopressin (treatment success)

Anticholinergics + Desmopressin

Imipramine

Imi + desmo

Laxatives

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