Bladder Dysfunction:

1) Enuresis ?
2) Nocturia ?
3) LUTS ?
4) Bladder dysfunction in CAKUT en CKD?

Johan Vande Walle.
L Dossche

Safepedrug IWT 130033,
Frederik Paulson chair

Nocturnal enuresis

Is it nephrology ??

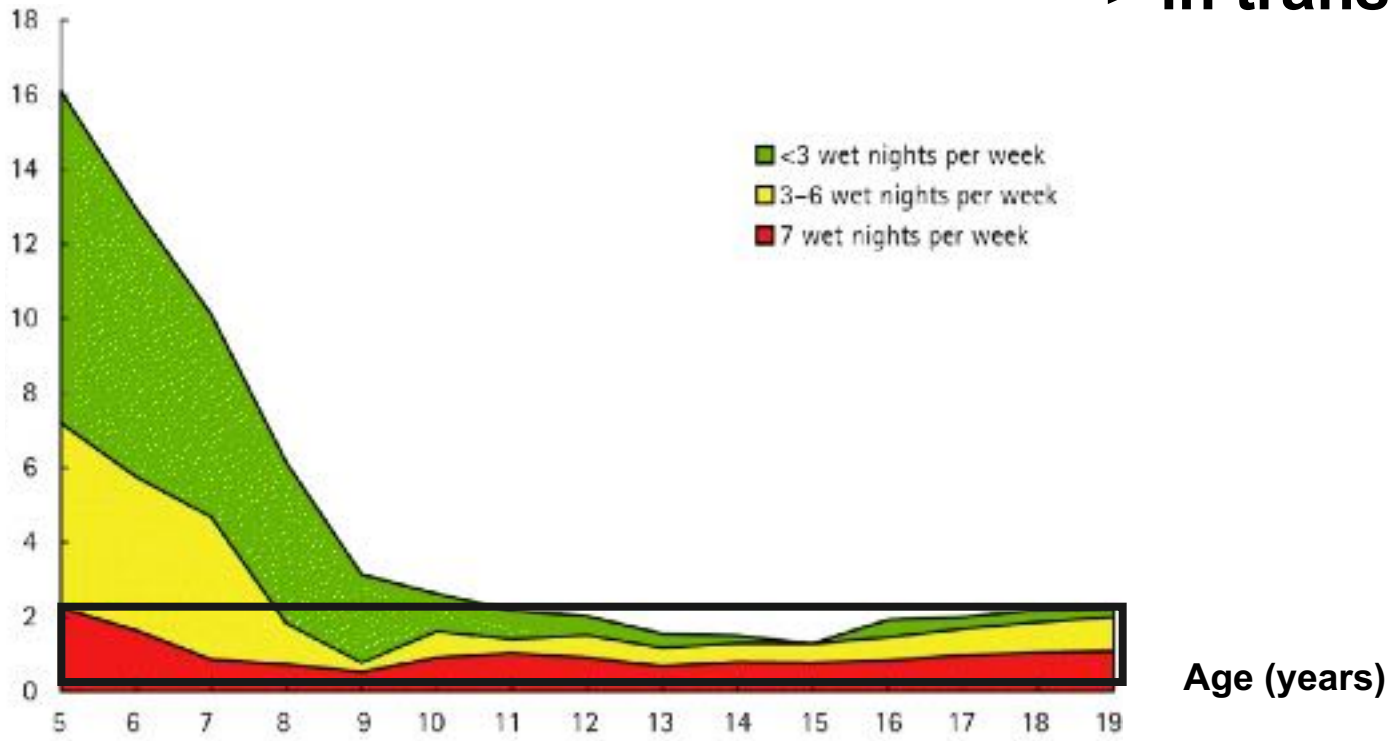
UZ GENT

UNIVERSITEIT GENT

1. Epidemiology

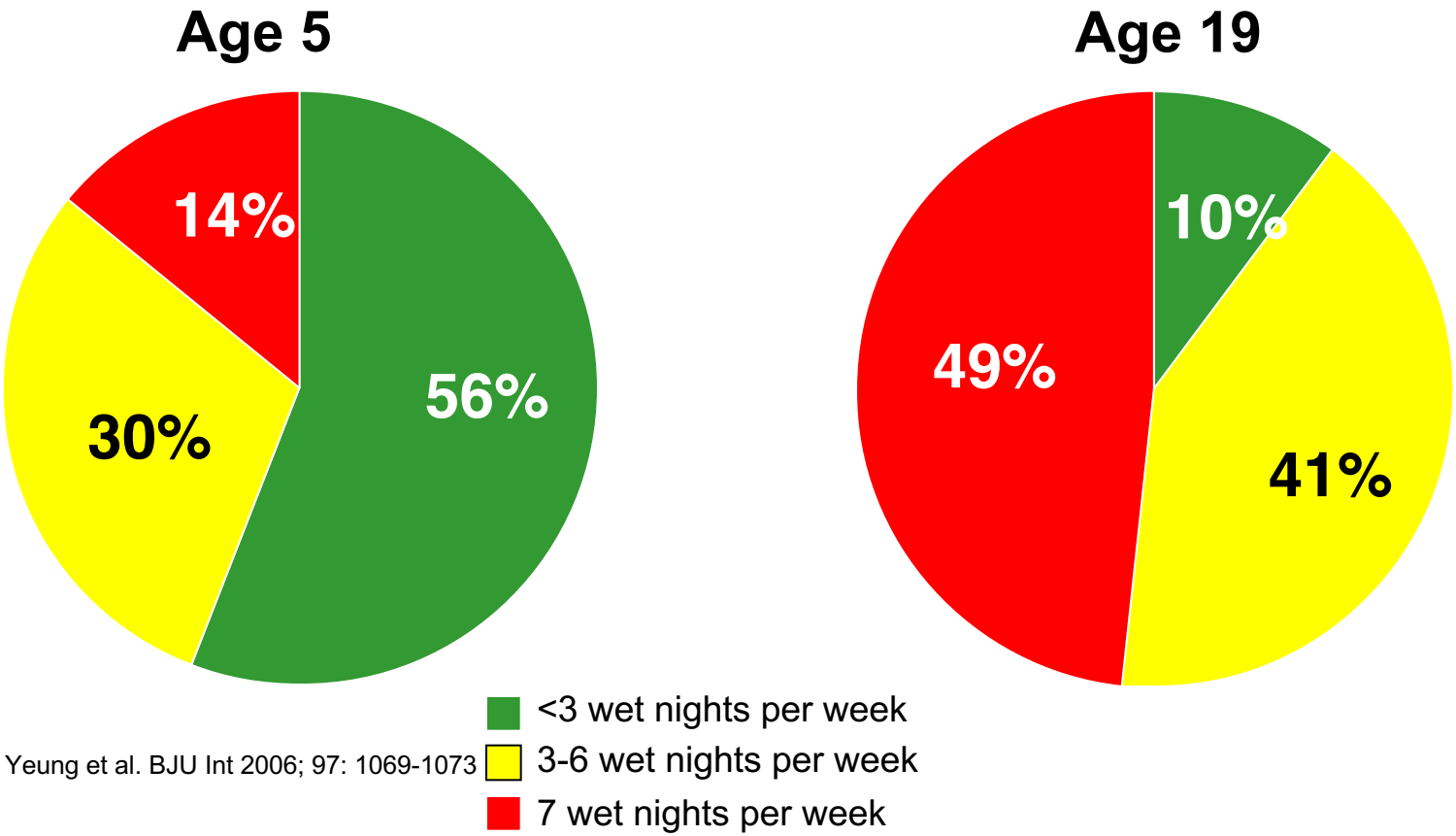
Severe Bedwetting

- **is persistent**
- **> congenital uropathies**
- **> in CKD**
- **> in transplants**



YEUNG, CHUNG K., SREEDHAR, BIJI, SIHOE, JENNIFER D.Y., SIT, FRANCES K.Y. & LAU, JOSEPH. Differences in characteristics of nocturnal enuresis between children and adolescents: a critical appraisal from a large epidemiological study. *BJU International* **97** (5), 1069-1073.

1. Epidemiology



Yeung et al. BJU Int 2006; 97: 1069-1073

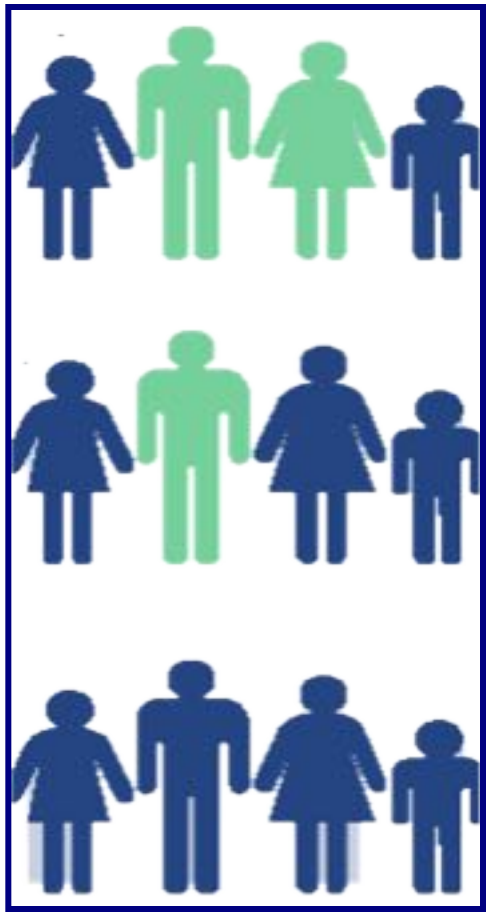
Enuresis

PATHOGENESIS /changing ideas

UZ GENT

UNIVERSITEIT GENT

Parental history



- 77% risk where both parents had been enuretics as a child
- 43% risk where only one parent had been enuretic as a child
- 15% risk where there is no parental history of enuresis
- 40% siblings also had PNE

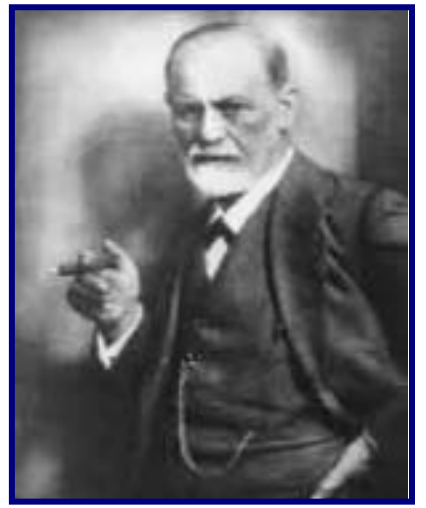
Bakwin. *Am J Dis Child* 1971;121;222–225; Jarvelin et al. *Acta Paediatr Scand* 1988;77:148–153

Molecular genetics

- Linkage studies have identified different genetic loci associated with PNE on chromosomes 4, 8, 12, 13 and 22
- Genetic heterogeneity
- Importance of CNS neurotransmitter genes / clock “genes” ?

Identification of genetic loci associated with nocturnal **enuresis**: a genome-wide association study.Jørgensen CS, JH.Lancet Child Adolesc Health. 2021 Mar;5(3):201-209

S. FREUD



Enuresis Nocturna

Before 1989

- Nocturnal enuresis
  - Was a benign condition
    - Not harming anybody
  - Self-limiting.. since it disappeared spontaneously
  - Not necessary to treat, except in rare cases
  - it was generally accepted that if there was a cause.. it had to be a psychological cause

2020 in primary enuresis:

- **NEVER a psychological cause**
- Psychological comorbidity / neurocognitive dysfunctions
- Psychological consequences
- no difference in primary or secondary
- It is not because psychotherapy might help, that it is a psychological cause

1989-2009

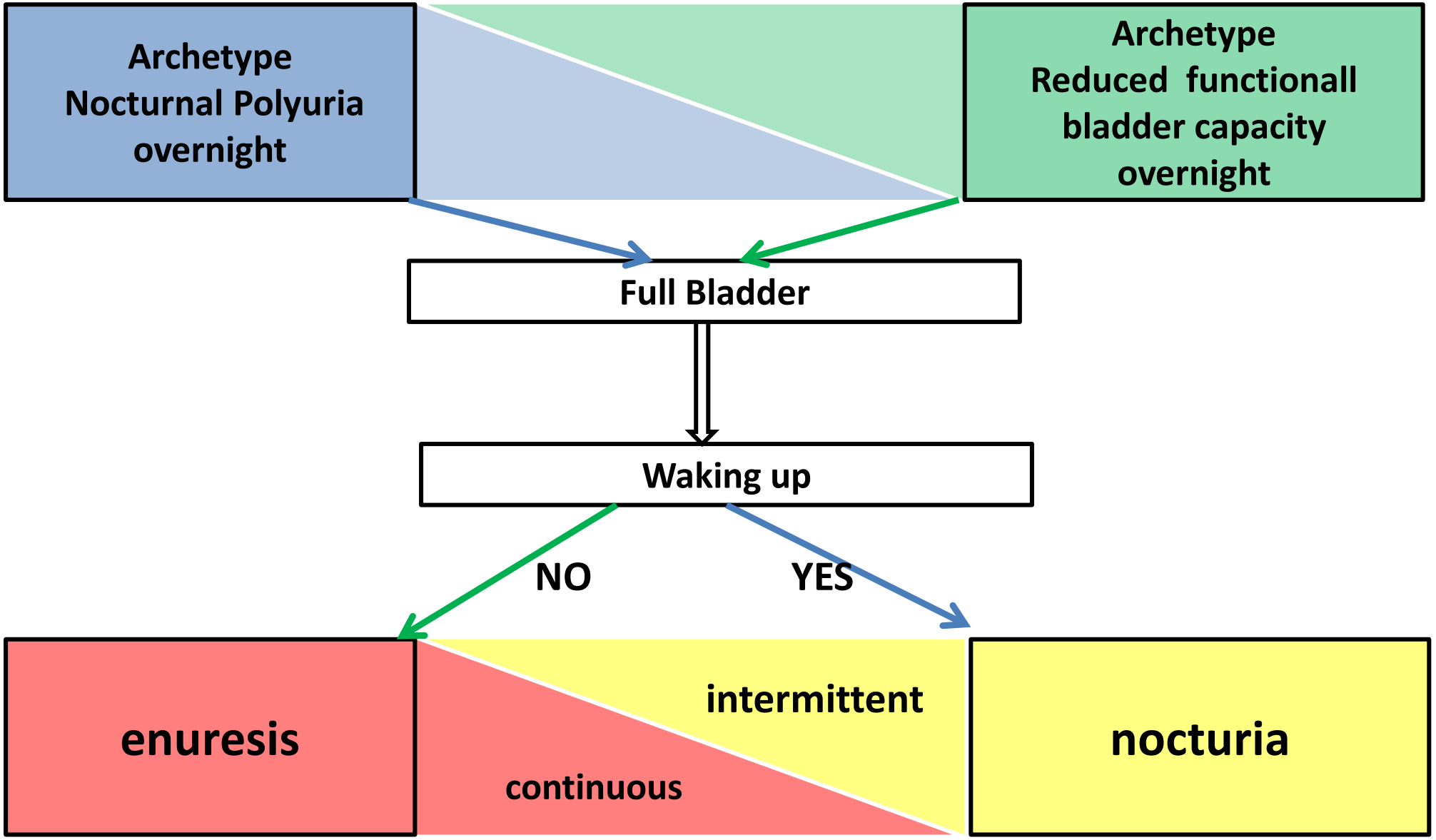
- enuresis is an organic condition
  - Caused by hereditary factors
  - Subdivided into 2 archetypes
    - Non monosymptomatic / monosymptomatic enuresis
- Where MNE is characterized by
  - A mismatch between nocturnal diuresis volume and functional bladder volume
  - Only spontaneously disappearing in mild cases, without comorbidity factors
  - With psychological consequences for child and family
  - discussion desmopressin versus alarm as treatment of choice

MNE+NP

MNE+OAB

MONOSYMPTOMAC VERSUS NON-MONOSYMPTOMATIC

- Non monosymptomatic enuresis : Bladder
  - Daytime Incontinence
  - Urgency
  - Frequency
  - Daytime symptoms
  - postponing
- Monosymptomatic enuresis
  - Bladder
    - Sometimes only during the night OAB (CK Yeung)
    - Apparent when increased fluid intake
  - Nocturnal diuresis
  - arousal
- Formula Hjalmas (Age+1)*30 ml


Archetype
Nocturnal Polyuria
overnight
Archetype
Reduced functionall
bladder capacity
overnight
Full Bladder
Waking up
NO
YES
enuresis
continuous
intermittent
nocturia

Enuresis archetype I : Bladderdysfunction OAB +++

Bladder dysfunction: heterogeneous disease

- Filling phase
- Detrusor
  - Overactive bladder = 90%
  - Underactive bladder = Lazzy bladder
  - Compliance
  - Combination

- Emptying phase
- Sphincter complex
  - Autonomous sphincter
  - Pelvic floor
  - Bladder neck
  - Urethra

- organic
- Functional
  - Various nervous systems involved
    - Cholinergic
    - Adrenergic
    - ..

Enuresis / LUTS +/- Bladder dysfunction

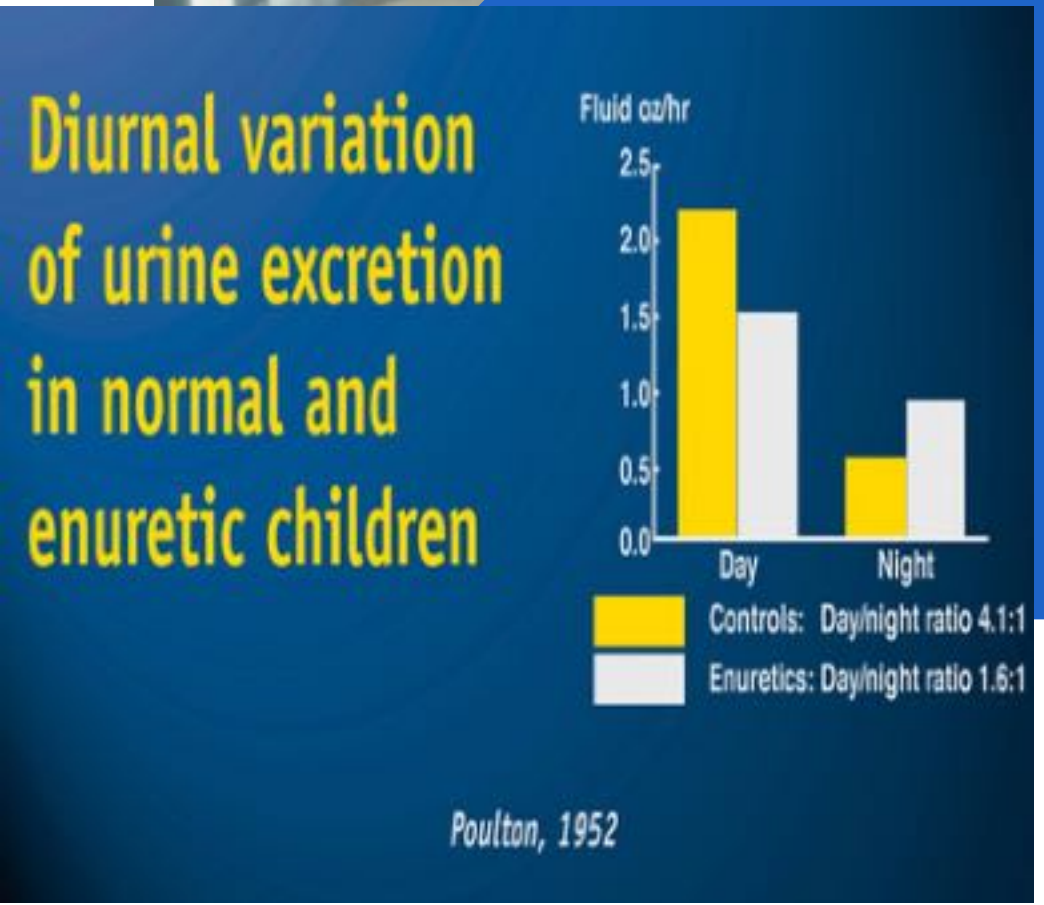
WAIT and SEE attitude

In renal diseases

- UTI
- Dysplasia
- CAKUT
  - Reflux
  - Persistant ureteral valves
  - Urethral valve bladder
- Renal transplants
- Bladder dysfunction

In neuropsychological disorders

- Autism /ADHD / MBD
- Disrupted sleep
- Neurogenic bladddder
- Non neurogenic neurogenic bladder
- Cerebral palsy
- Metabolic and neurological diseases



SAFE PEDRUG

Enuresis archetype II: Nocturnal polyuria

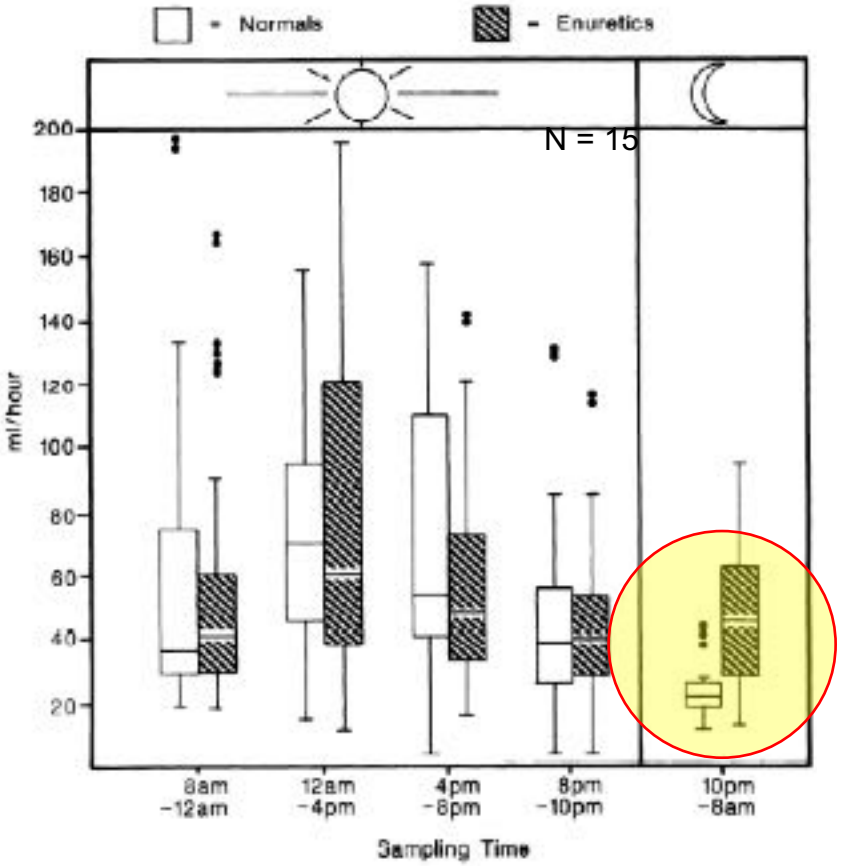
Nocturnal polyuria and enuresis

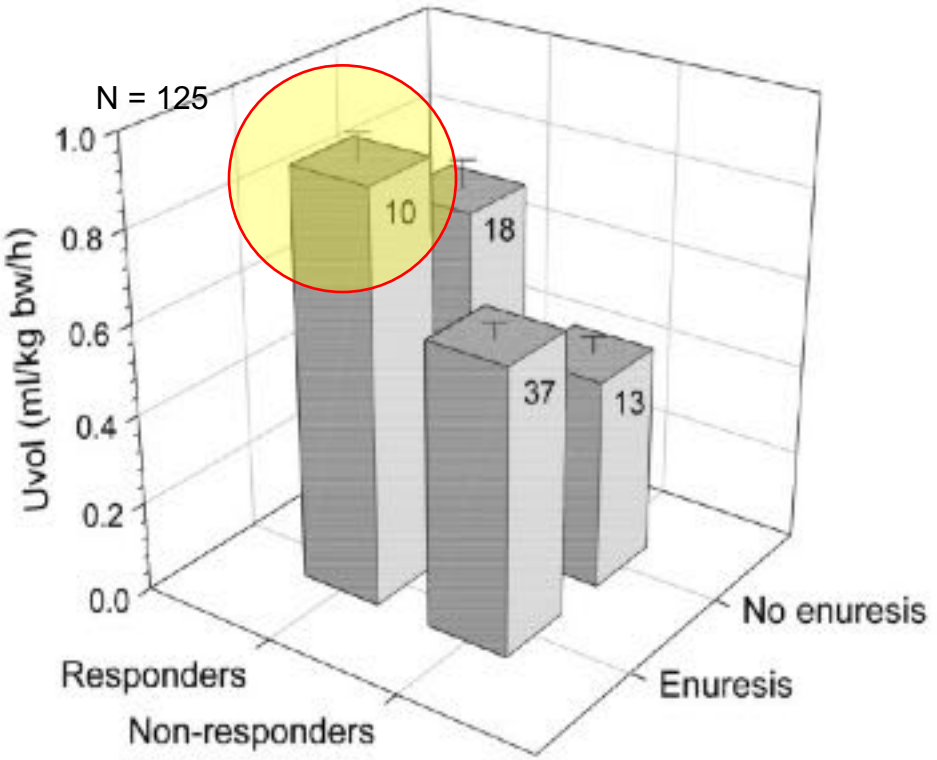
- Formula Hjalmas : (age+1)*30ml with maximum 300 ml

- >130% = polyuria definition= ICCS standardisation

- >100%... Likely desmopressin sensitive

Nocturnal polyuria in enuresis

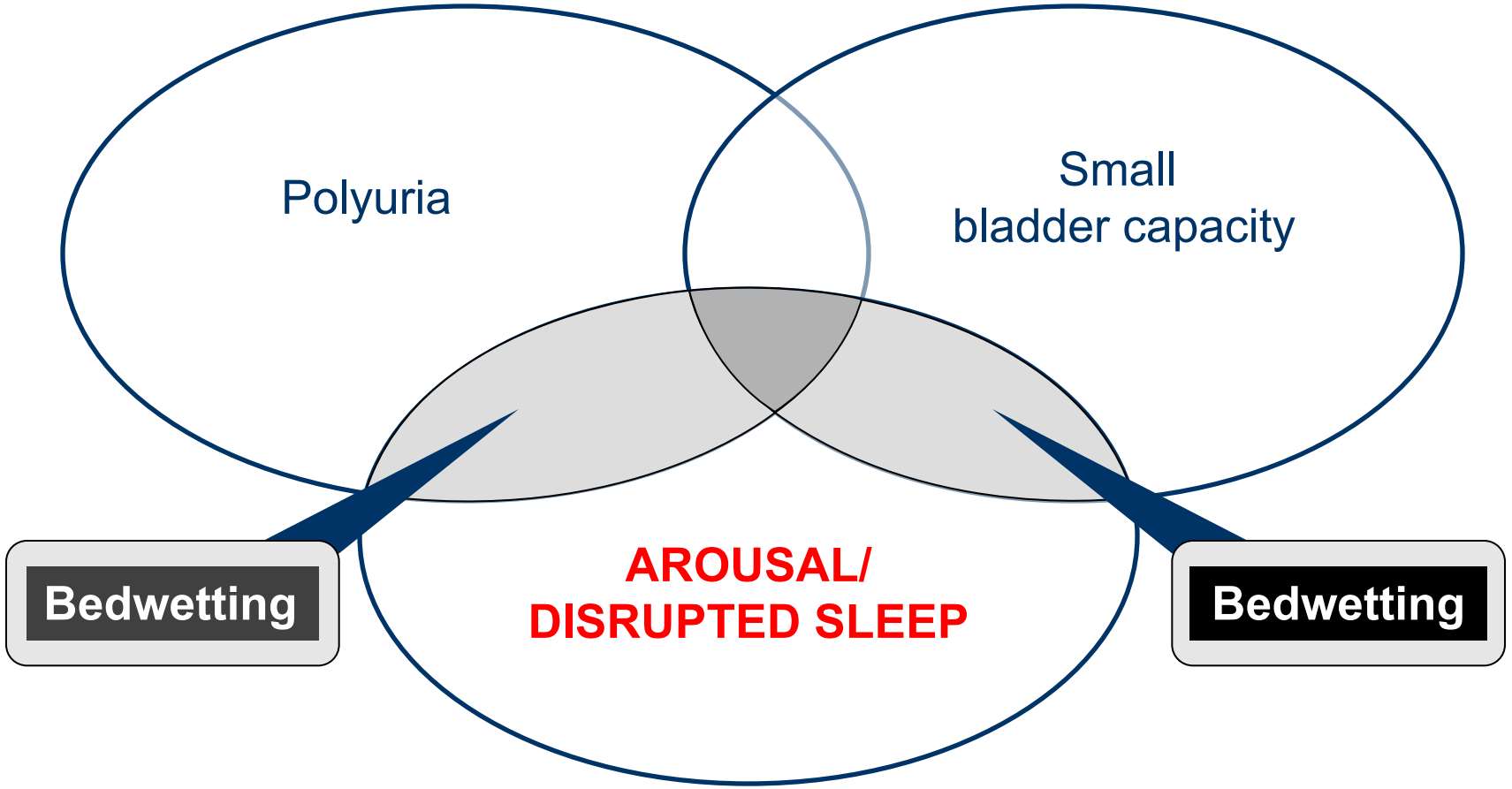




Rittig et al, Am J Physiol, 1989

Rittig et al, J Urol, 2008

Bedwetting Occurs as a Result of Two or More Causes



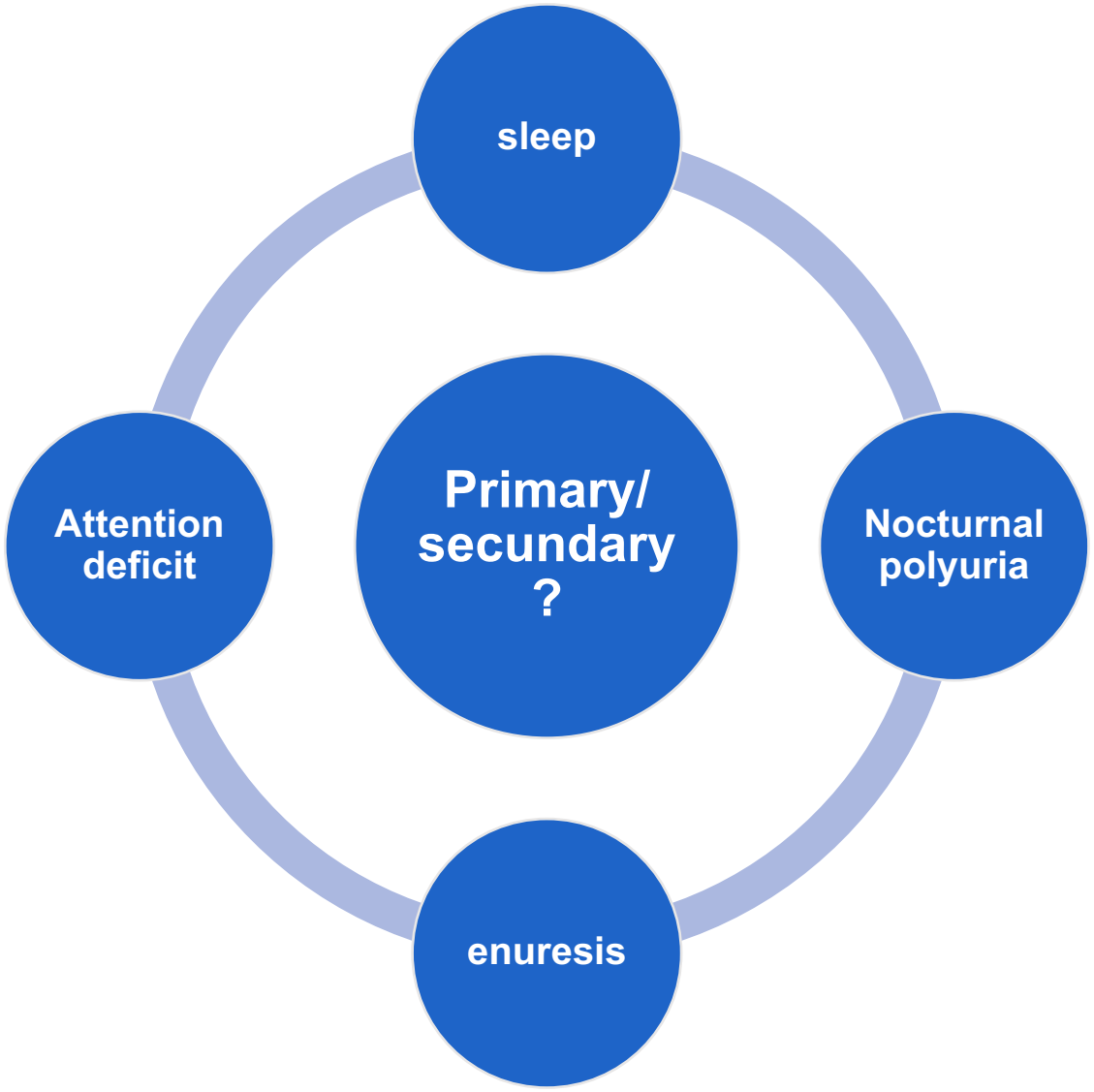
Johan Vande Walle

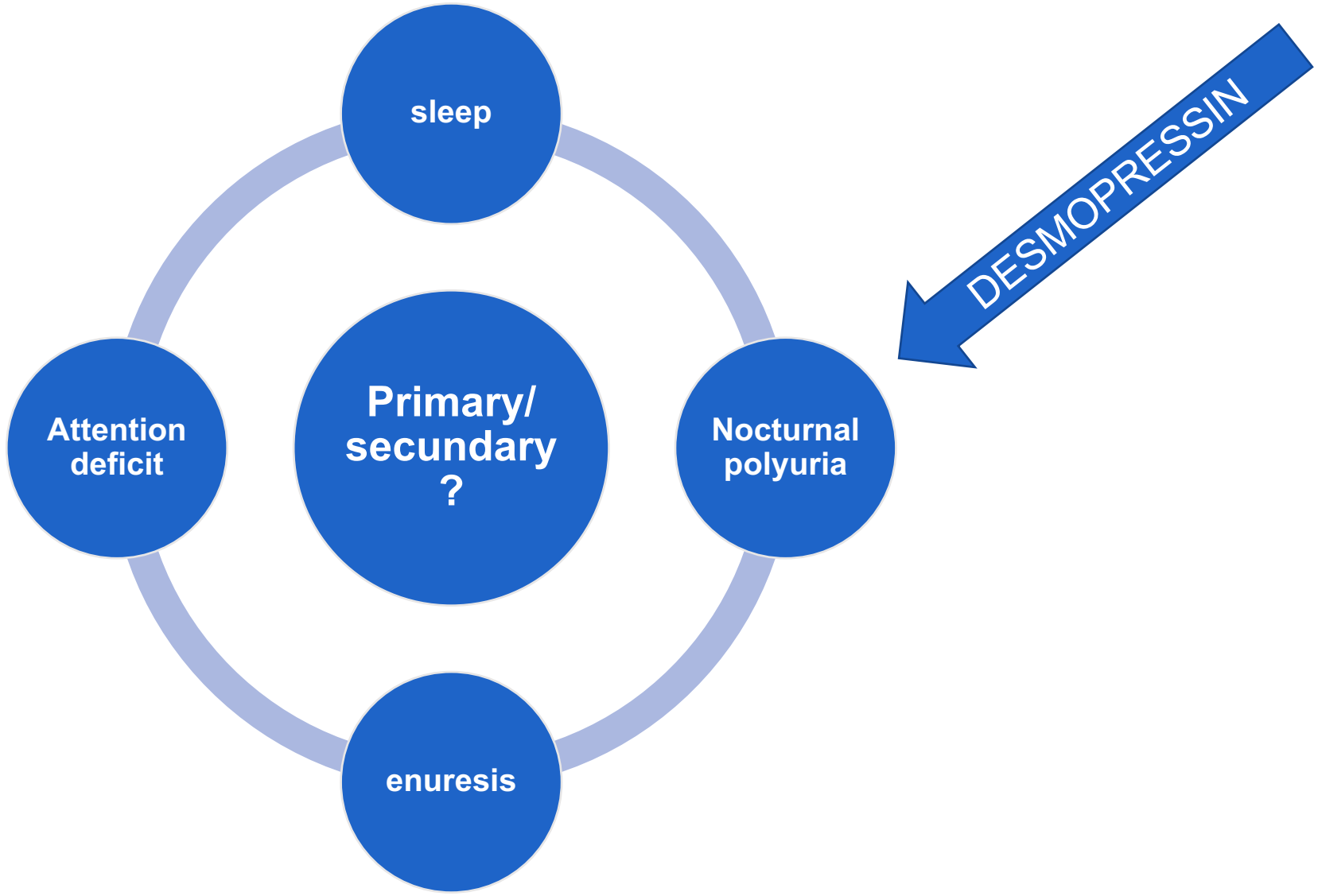
Enuresis

Why to treat ?

- Burden for parents and child
- Psychological consequences

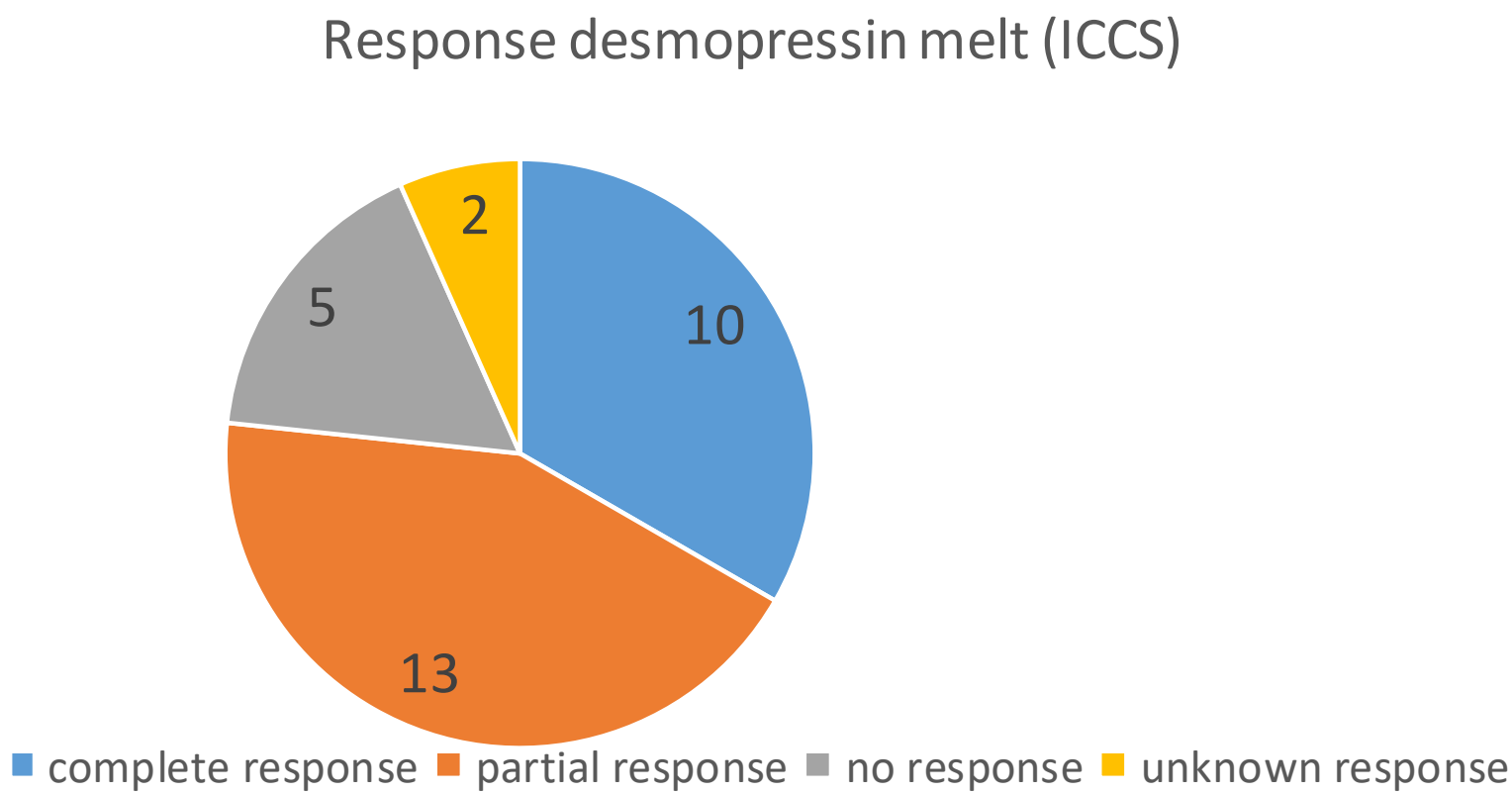
UZ GENT
UNIVERSITEIT GENT


sleep
Attention deficit
Primary/ secundary ?
Nocturnal polyuria
enuresis


sleep
Attention deficit
Primary/ secundary ?
Nocturnal polyuria
enuresis
DESMOPRESSIN

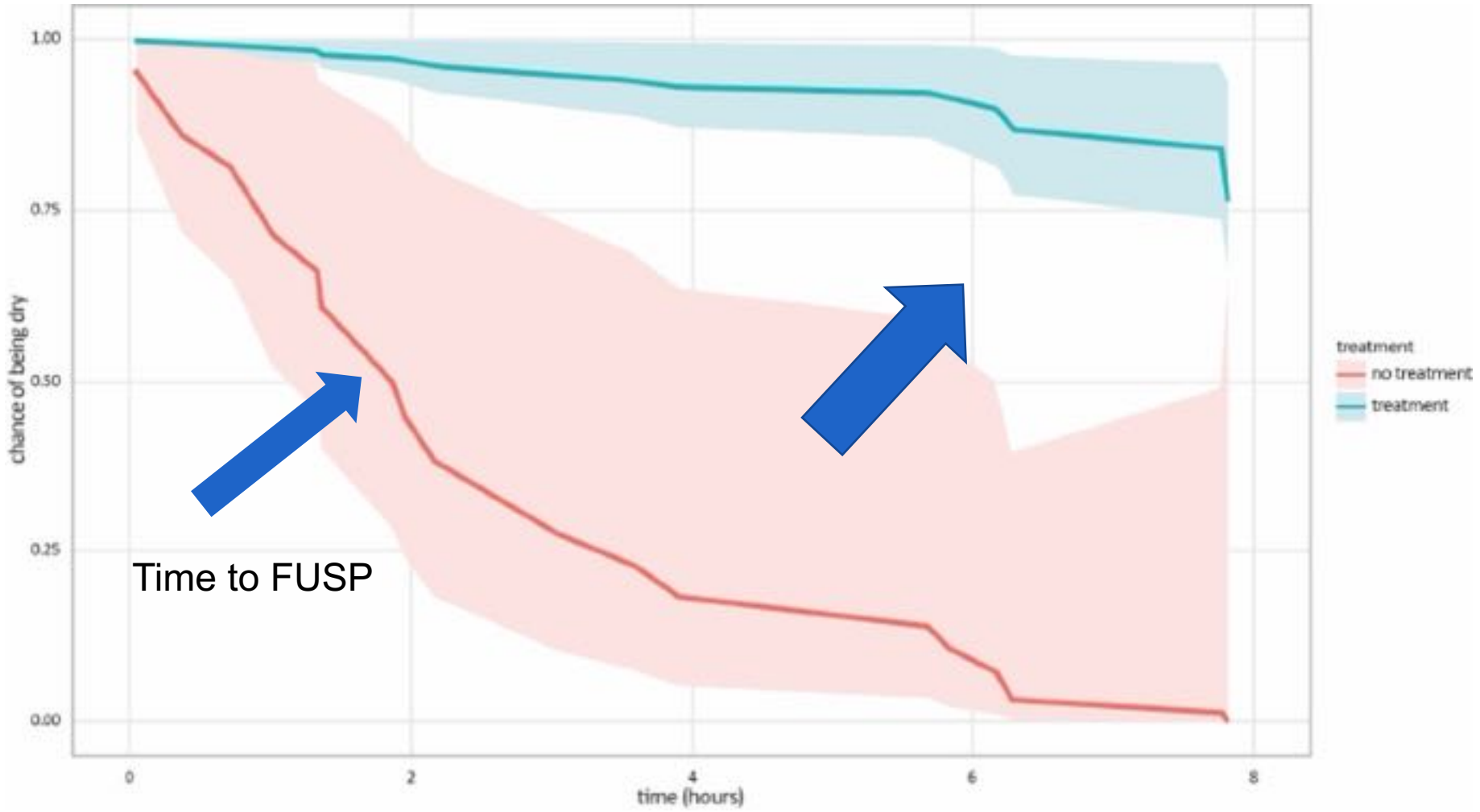
Response rate

Prospective study : response to desmopressin melt in children with MNE + NP



Enuretic parameters / sleep :
FUSP = first uninterrupted sleep period

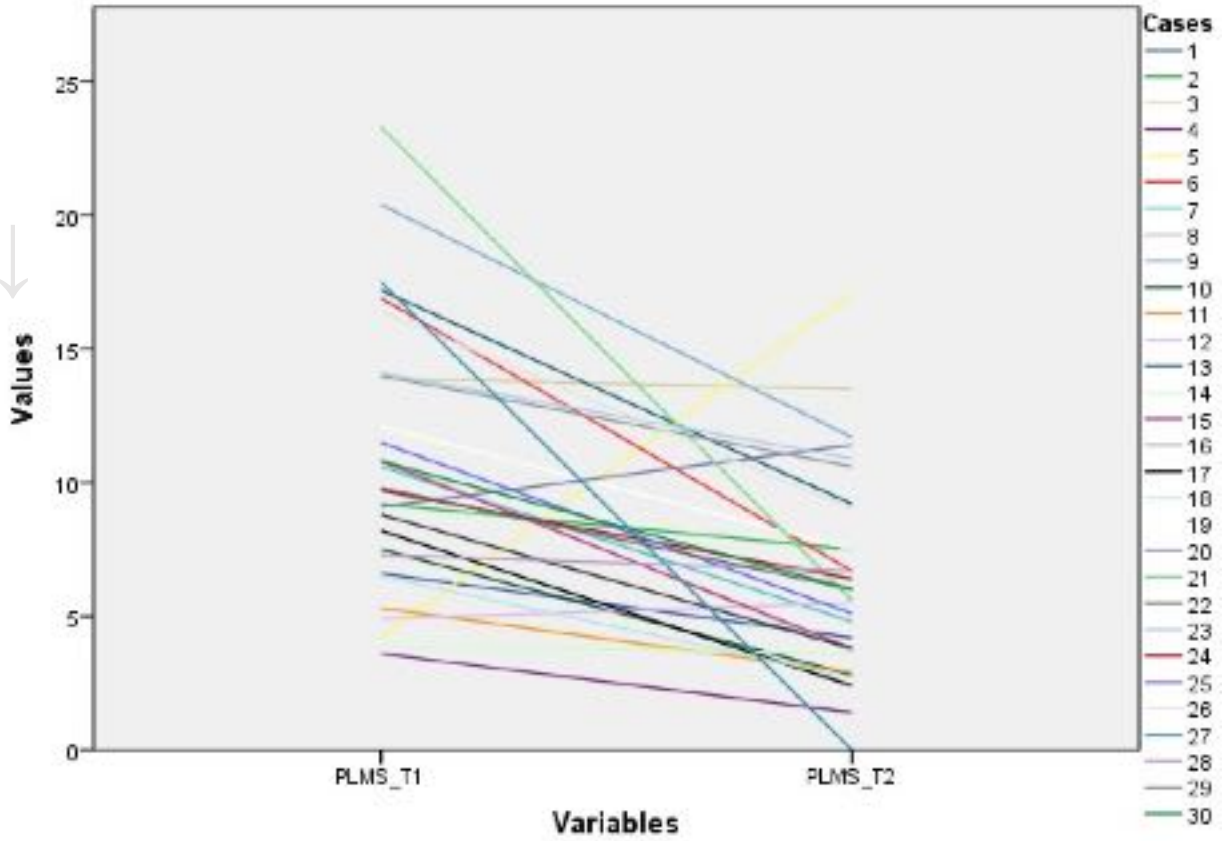
- Time alarm = FUSP



Results: Sleep : PLMS

- PLMS index

PLMS-index
(p<.001)



Enuresis is not a benign condition
Results of the sleep study

- Comorbidity with
  - Disrupted sleep
  - Restless legs symptoms
  - Attention deficit + psychology
  - Poor QOL
  - Burden to the patients
- Ameliorating during desmopressin therapy

Enuresis +/- Nocturnal polyuria

WAIT and SEE attitude

Enuresis +/- Nocturnal polyuria

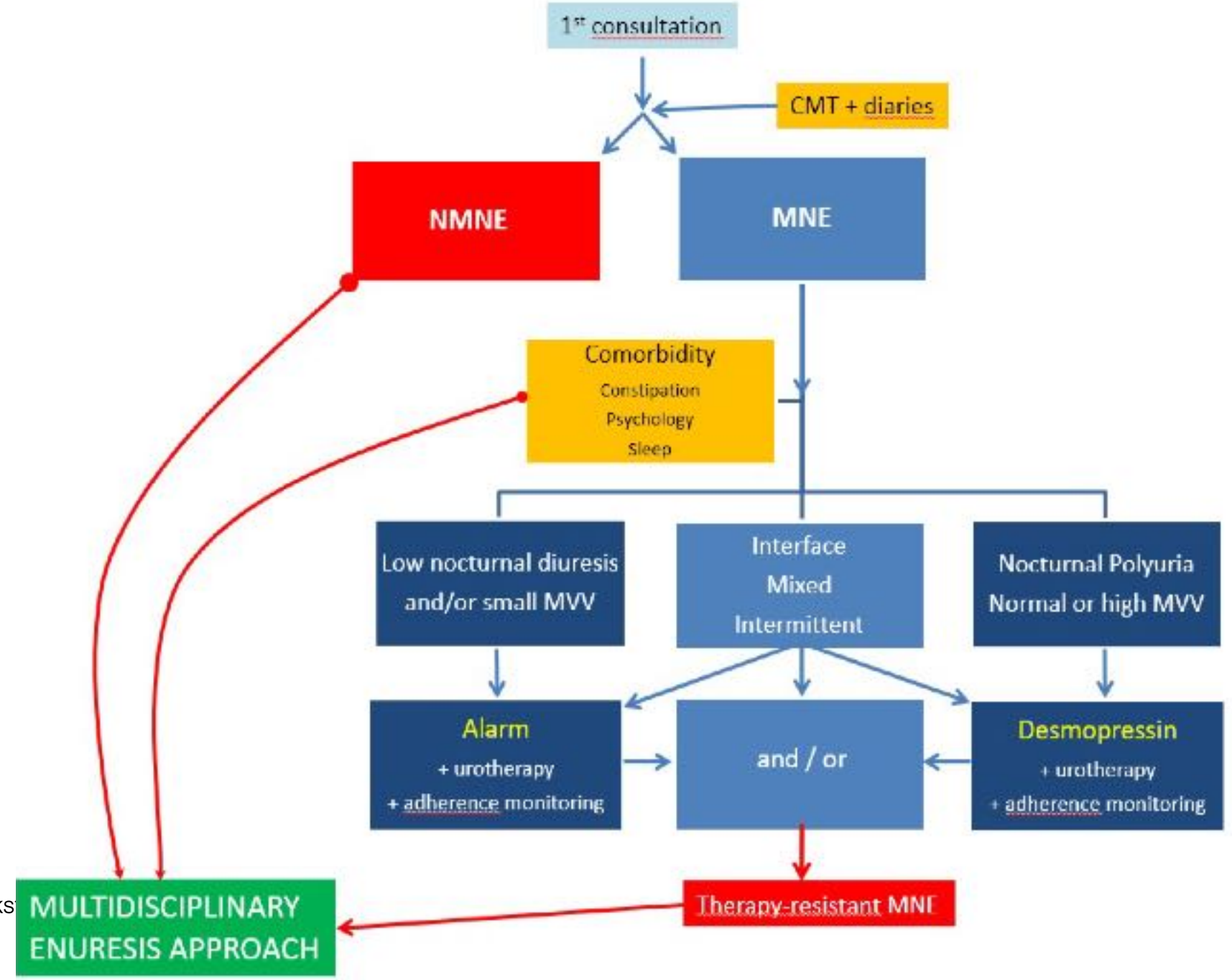
WAIT and SEE attitude

In renal diseases

- Tubular disorders
- CKD + deficient concentration
- Oedema
- Nocturnal Hypertension
- Renal transplants
- Bladder dysfunction
- Overnight nutrition
- Drugs (steroids, NSAID's, CsA..etc..)

In neuropsychological disorders

- Autism /ADHD
- Disrupted sleep
- Overnight nutrition


1st consultation
CMT + diaries
NMNE
MNE
Comorbidity
Constipation
Psychology
Sleep
Low nocturnal diuresis
and/or small MVV
Interface
Mixed
Intermittent
Nocturnal Polyuria
Normal or high MVV
Alarm
+ urotherapy
+ adherence monitoring
and / or
Desmopressin
+ urotherapy
+ adherence monitoring
Therapy-resistant MNE
MULTIDISCIPLINARY
ENURESIS APPROACH

Comorbidities

Nocturnal enuresis

- enuresis is an organic disease
  - A mismatch between diuresis volume and functional bladder volume overnight / hereditary (genes)
  - Associated with disrupted sleep pattern
  - “Only” spontaneously disappearing in mild cases
  - Importance of **comorbidity** factors
  - With **severe** psychological consequences
    - For child (selfesteem, burden), and and family (intolerance)
  - **making a wait and see attitude is not longer defendable**

Enuresis

How to treat ?

Practical guidelinesJ. Vande Walle, S.Bauer, S Tekgull, J Evans,S Rittig, P Eggert; Eur J Pediatrics 2012

UZ GENT

UNIVERSITEIT GENT

Signs and symptoms	Presence/ absence		Consider referral if positive (R)
Nocturnal enuresis	Yes	No	
Does the child wet the bed? • Number of nights per week ----------	Yes	No	
Establishes severity, which is suggestive of prognosis			
Age ≥5 years	Yes	No	
Younger patients are likely to experience spontaneous resolution without intervention; treatment only considered in children ≥5 years			

Symptoms suggestive for underlying bladder dysfunction			

Leakages of urine during the day
• Drops of urine in the underpants
  • Before voiding
  • After voiding
• Very wet underpants
• Frequency of leakage (N = episodes per day)
• Intermittent or continuous leakage every day?
• History of daytime incontinence over 3½ years of age
	Yes	No	R

Suggestive of overactive bladder/NMNE			
Urinary frequency (# of voids) (≥8 x/day)?	Yes	No	R
Suggestive of overactive bladder			
Voiding postponement (# of voids) (≤3 x/day)?	Yes	No	R
Suggestive of dysfunctional voiding			
Sudden and urgent need to urinate?	Yes	No	R
Suggestive of overactive bladder			
Holding maneuvers observed (e.g. Vincent's curtsey – pressing heel into perineum, leg crossing, standing on tiptoes)	Yes	No	R
Suggestive of dysfunctional voiding			
Needs to push in order to urinate, i.e. need to use abdominal muscles to strain to pass urine?	Yes	No	R
Suggestive of dysfunctional voiding			
Interrupted urinary stream, or several voids, one after another?	Yes	No	R
Suggestive of dysfunctional voiding			
History of urinary tract infection?	Yes	No	R
Often associated with underlying bladder dysfunction			
Illness and/or malformation?			
• Of kidneys and/or urinary tract	Yes	No	R
• Of spinal cord	Yes	No	R

Comorbidity – factors that might predict therapy resistance			
Bowel movements – presence or history of the following? • Constipation (≤3 bowel movements/week) • Traces of feces in the underpants (fecal incontinence) – not due to insufficient wiping of the bottom?	Yes	No	See Box 3; may be treated in primary care
May predict treatment resistance; resolution of constipation may resolve enuresis			
Psychological, behavioral or psychiatric problems? • Evidence of ADHD, ADD, autism, etc	Yes	No	R
May predict treatment resistance			
History of motor and/or learning disabilities or delayed development			
Delayed development may be suggestive of central nervous system pathology			
Drinking habits			
• Quantity and type of fluid intake? • Drinks more than one glass during the evening? • Drinks during the night?	 Yes Yes	 No No	
Water turnover in children is reported to be 1500 ml/m^2 body surface area per day[42] Fluid intake in the evening (after the evening meal) should be minimized since increased fluid intake results in higher diuresis volumes during the night Fluid intake during the night should be avoided			
Exclude diabetes mellitus (dipstick test) Psychogenic polydipsia poses risk for water intoxication with desmopressin			

comorbidity in “refractory enuresis”

- May interfere with response-rate
  - Combined disorder
  - Constipation/ fecal incontinence (Y. Homsy)
  - History of UTI, uropathy,
  - Thick bladder wall (CK Yeung)
  - ADHD, ADD, autism (Baeyens, von Gontard)
  - Mentally and motoric disability (Van Laecke)
  - Psychological problems *(E Vanhoecke J Urol 2006)*
  - Sleeping disorders (snorring, waking up, restless legs, talking in sleep (CK Yeung, Dhont)

Step 1

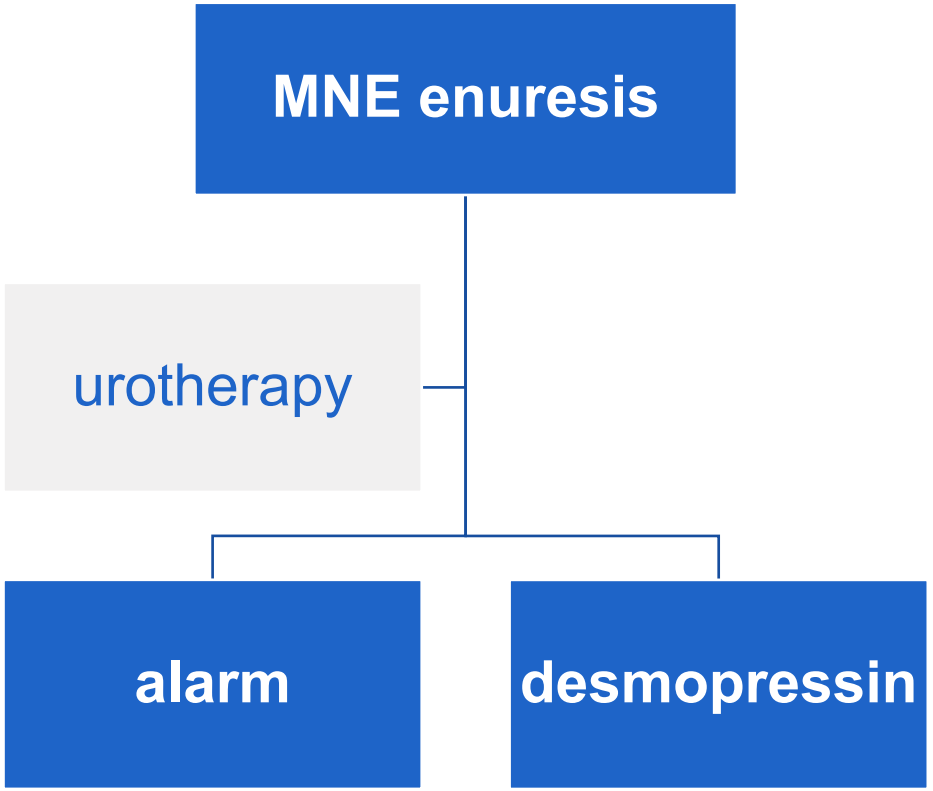
- Step 1 Urotherapy advice
- Step 2 based on clinical management tool

Step 1

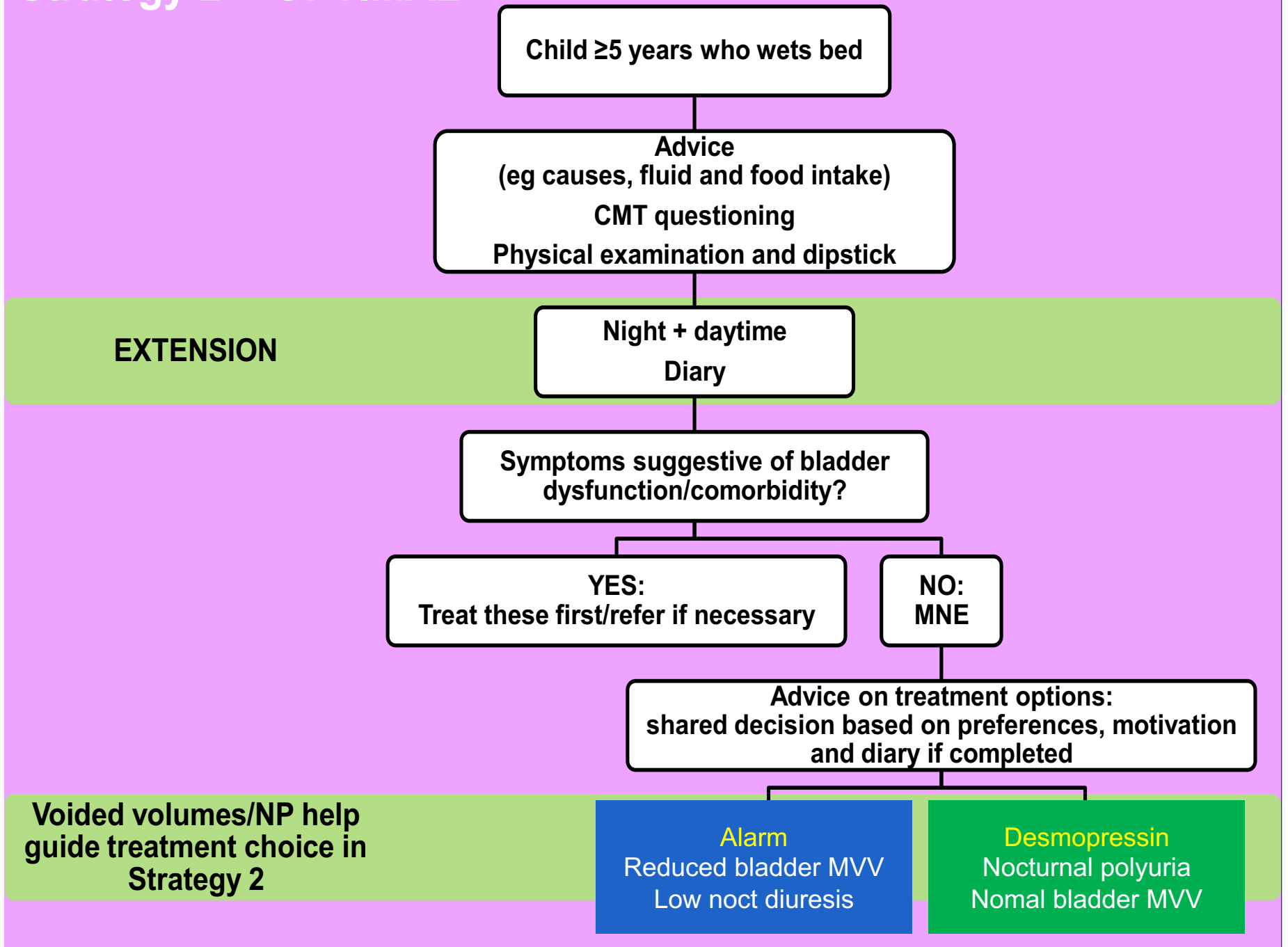
NO EVIDENCE

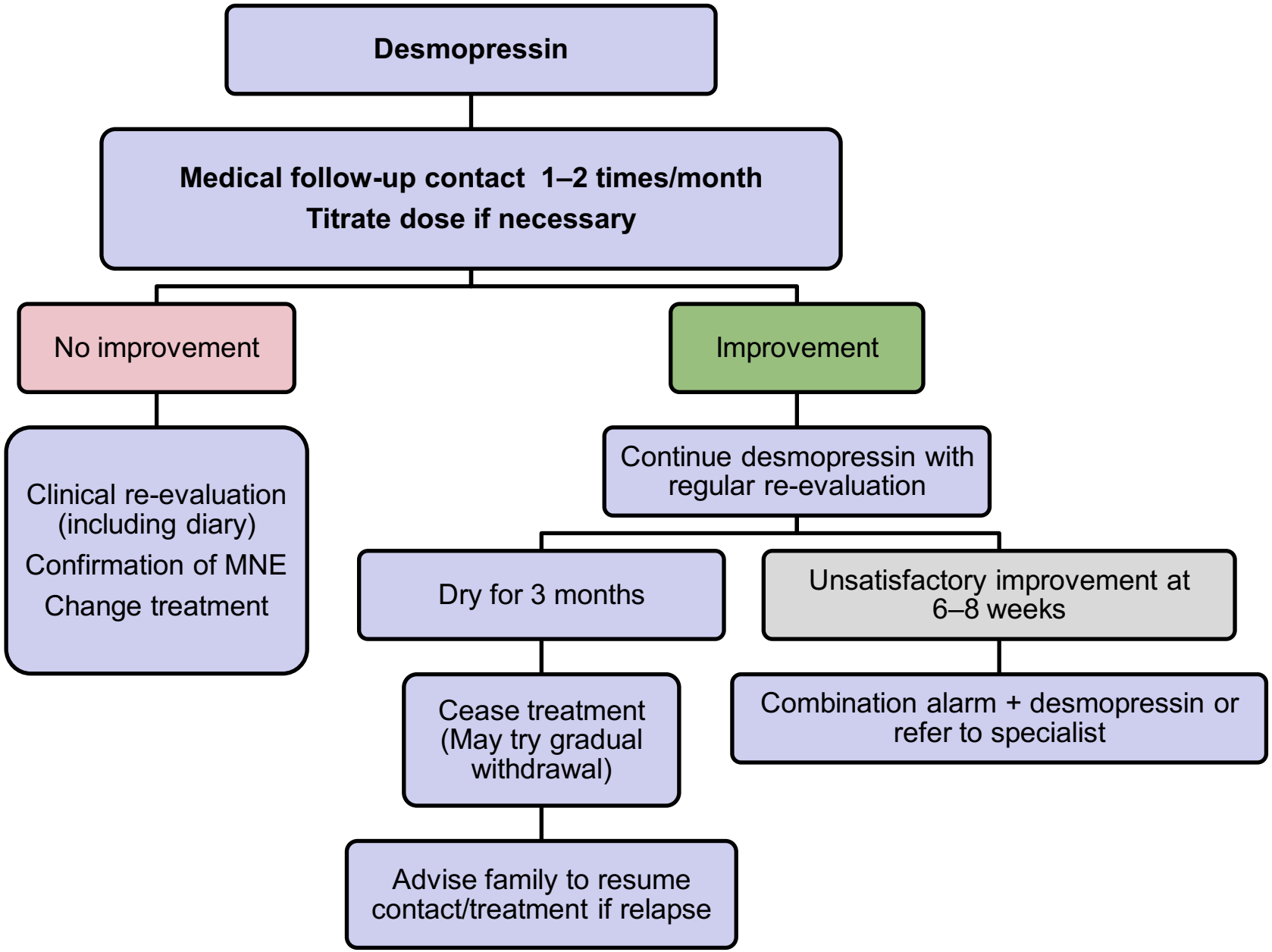
- Step 1 Urotherapy advice
- Step 2 based on clinical management tool

- MNE is that MNE:


MNE enuresis
urotherapy
alarm
desmopressin

Strategy 2 = OPTIMAL




Desmopressin
Medical follow-up contact 1–2 times/month
Titrate dose if necessary
No improvement
Improvement
Clinical re-evaluation (including diary)
Confirmation of MNE
Change treatment
Continue desmopressin with regular re-evaluation
Dry for 3 months
Unsatisfactory improvement at 6–8 weeks
Cease treatment (May try gradual withdrawal)
Combination alarm + desmopressin or refer to specialist
Advise family to resume contact/treatment if relapse

Overactive bladder: treatment : first treat daytime symptoms : consensus…but EBM weak

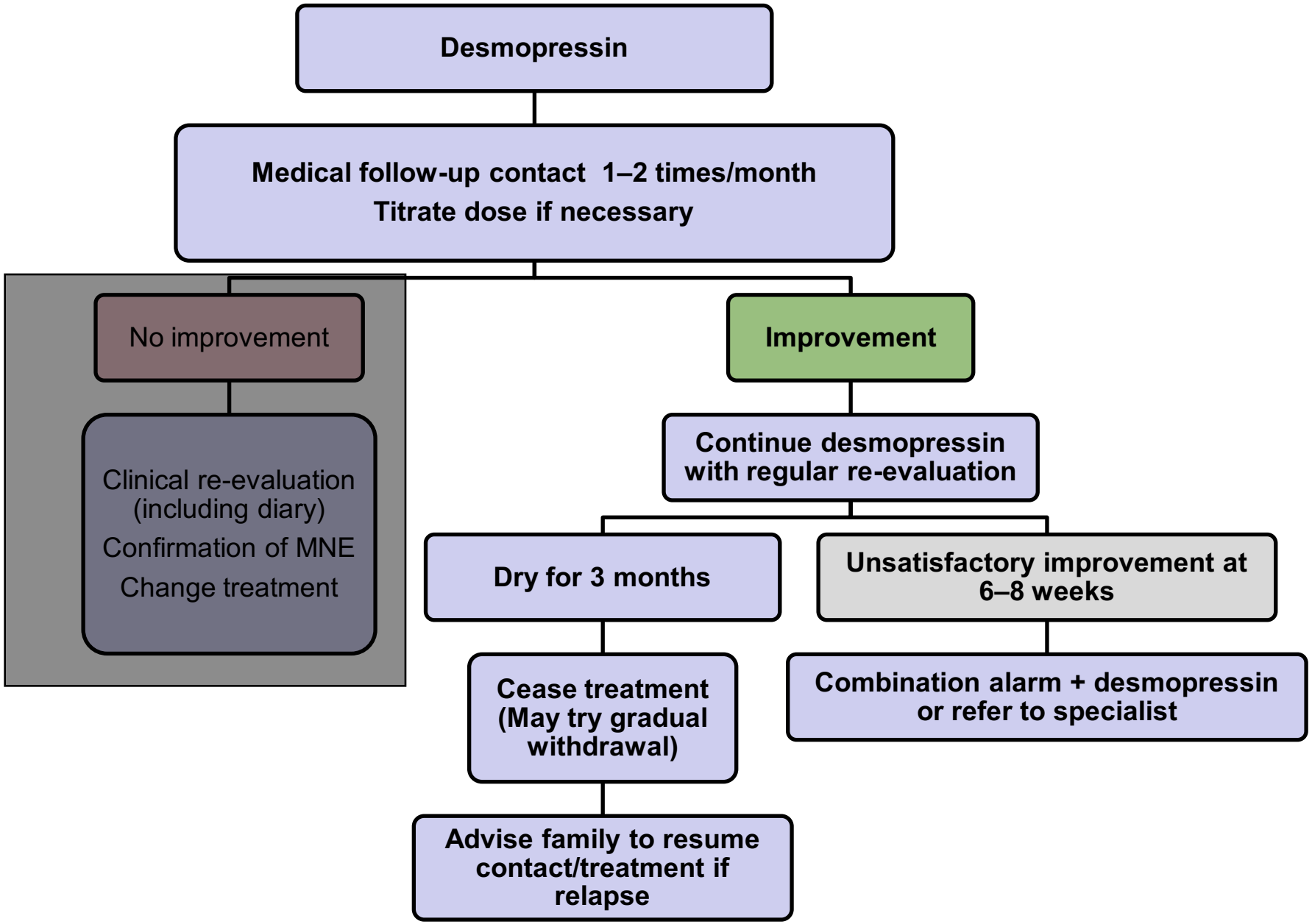
- **Classic**

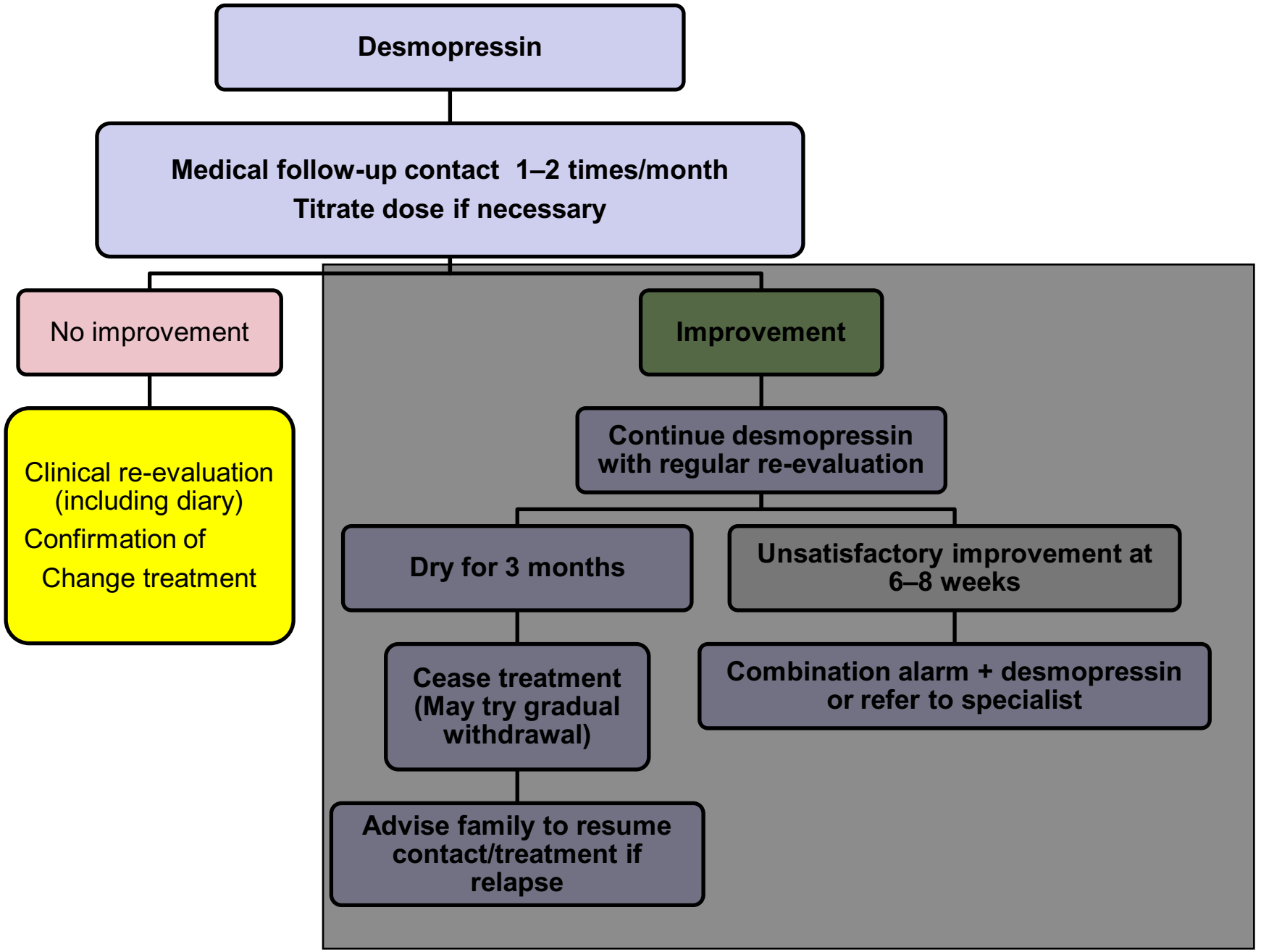
Urotherapy

- Antimuscarinics:
  - Oxybutinin: non-selective : 0,3-0,6 mg/kg/d in 3 doses
  - Tolterodine: non-selective: 0,5-2 mg/day
  - Solifenacin: M2 M3 : 1,25-10mg/day
  - Propiverine: non-selective: 0,4-0,8mg/kg/day in 2 doses
  - Trospium: non-selective: 10-25mg/d in 2 doses
- A-blockers:
  - Doxazosin, tamsulosin, terazosin
- Tricyclic antidepressant: imipramine

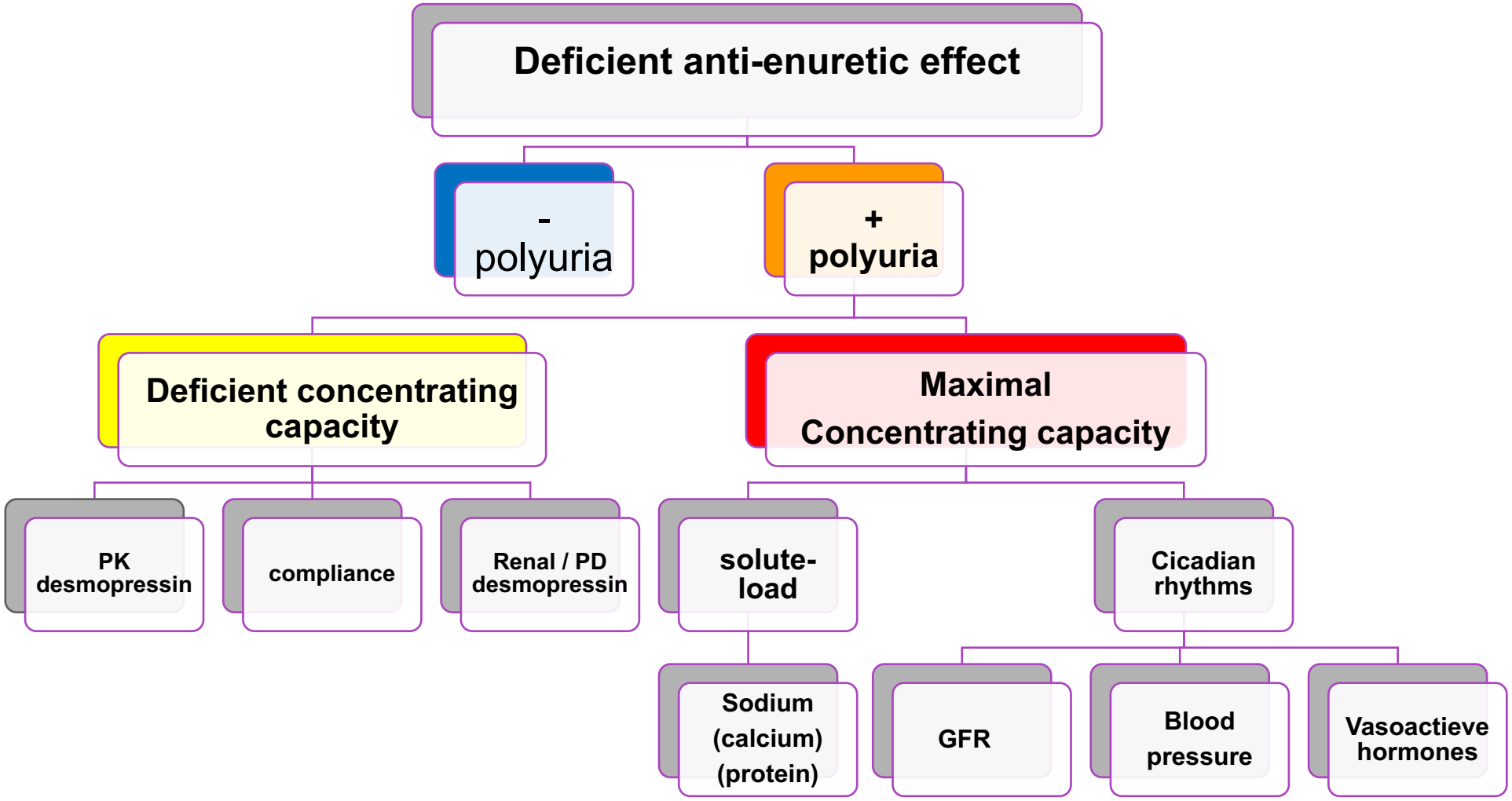
- **New**

- Antimuscarinics:
  - **Fesoterodine**
- B3-adrenoreceptor agonist
  - **Betmiga**
- Botulinum toxin
- Neuromodulation (Tens/Pens/inplant)
- Reuptake inhibitor of serotonin and norepinephrine
  - **Duloxetine /Reboxitine**
- Filling rate bladder
- Voiding school / camps


Desmopressin
Medical follow-up contact 1–2 times/month
Titrate dose if necessary
No improvement
Clinical re-evaluation (including diary)
Confirmation of MNE
Change treatment
Improvement
Continue desmopressin with regular re-evaluation
Dry for 3 months
Cease treatment (May try gradual withdrawal)
Advise family to resume contact/treatment if relapse
Unsatisfactory improvement at 6–8 weeks
Combination alarm + desmopressin or refer to specialist


Desmopressin
Medical follow-up contact 1–2 times/month
Titrate dose if necessary
No improvement
Clinical re-evaluation (including diary)
Confirmation of
Change treatment
Improvement
Continue desmopressin with regular re-evaluation
Dry for 3 months
Unsatisfactory improvement at 6–8 weeks
Cease treatment (May try gradual withdrawal)
Combination alarm + desmopressin or refer to specialist
Advise family to resume contact/treatment if relapse

Desmopressin resisistant nocturnal polyuria



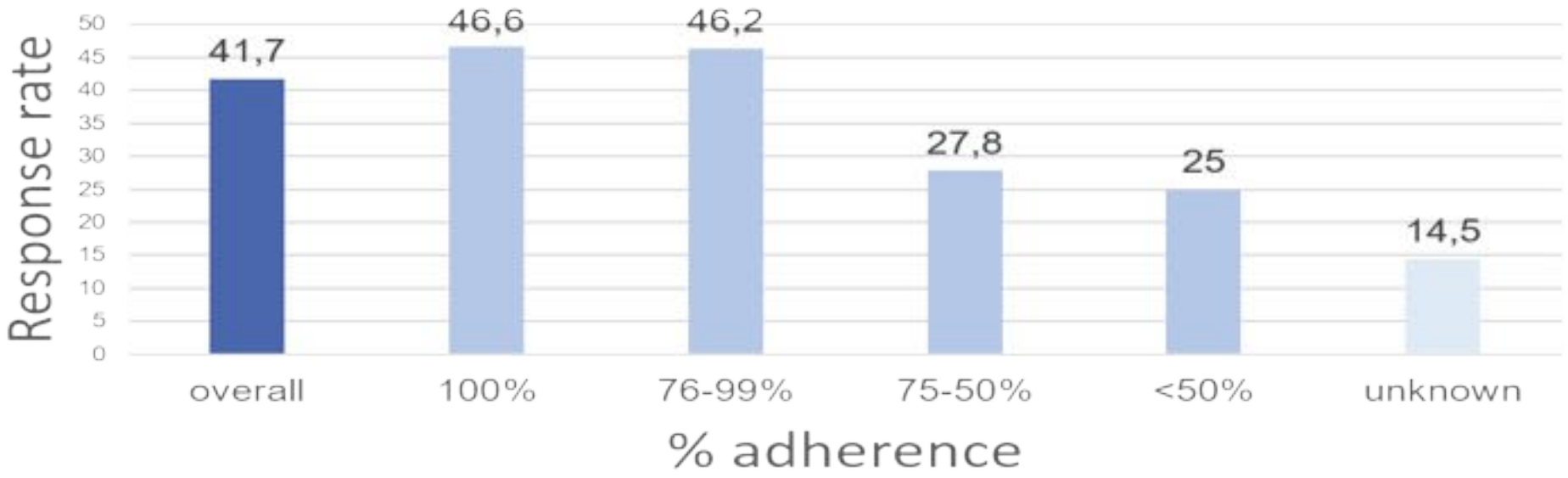
1. ADHERENCE

1. ADHERENCE

?

Poor Compliance With Primary Nocturnal Enuresis Therapy May Contribute to Insufficient Desmopressin Response

Charlotte Van Herzeele, Ilona Alova, Jonathan Evans, Paul Eggert,*
Henri Lottmann,* Jens Peter Nørgaard and Johan Vande Walle†,‡



0022-5347/09/1824-2045/0
THE JOURNAL OF UROLOGY®

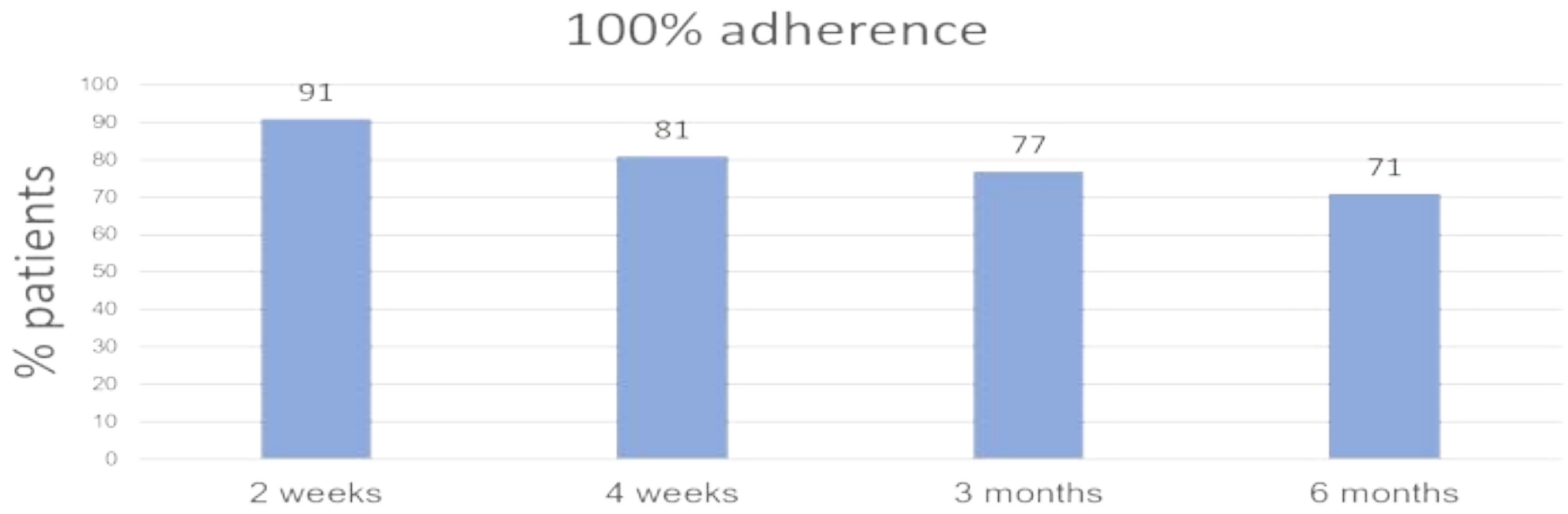
Vol. 182, 2045-2049, October 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2009.06.001

www.jurology.com

1. ADHERENCE

Poor Compliance With Primary Nocturnal Enuresis Therapy May Contribute to Insufficient Desmopressin Response

Charlotte Van Herzeele, Ilona Alova, Jonathan Evans, Paul Eggert,*
Henri Lottmann,* Jens Peter Nørgaard and Johan Vande Walleț,‡



0022-5347/09/1824-2045/0
THE JOURNAL OF UROLOGY®

Vol. 182, 2045-2049, October 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2009.06.001
www.jurology.com

2.Optimize urotherapy

- Diet advice
  - Normal protein and sodium intake diet
  - Spreading over the day
  - Avoid highest osmotic load in the evening
  - No food after evening meal
- Evidence ??? NO
- Rationale with indirect evidence : Yes

Fig1

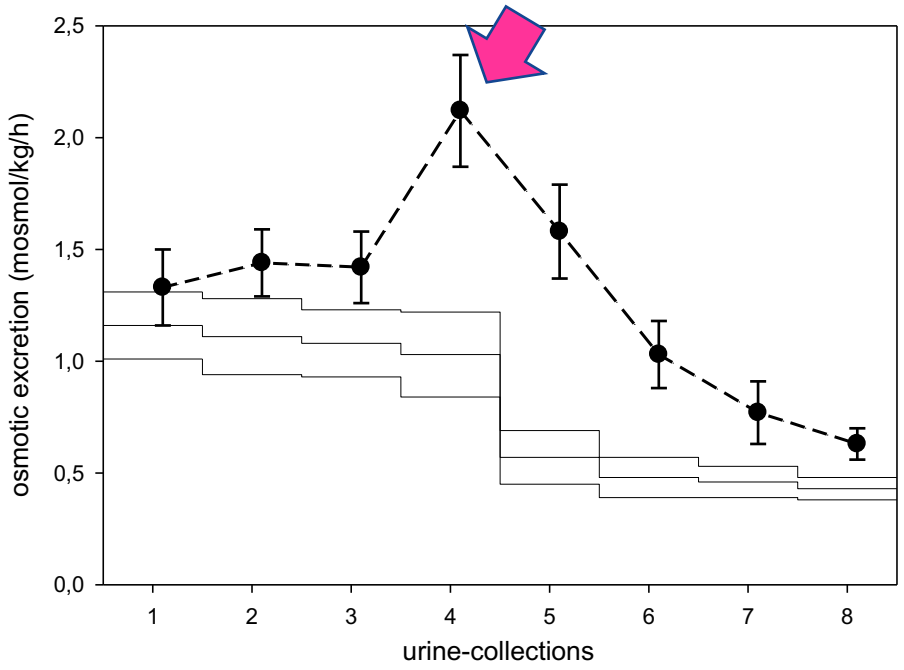


Fig2

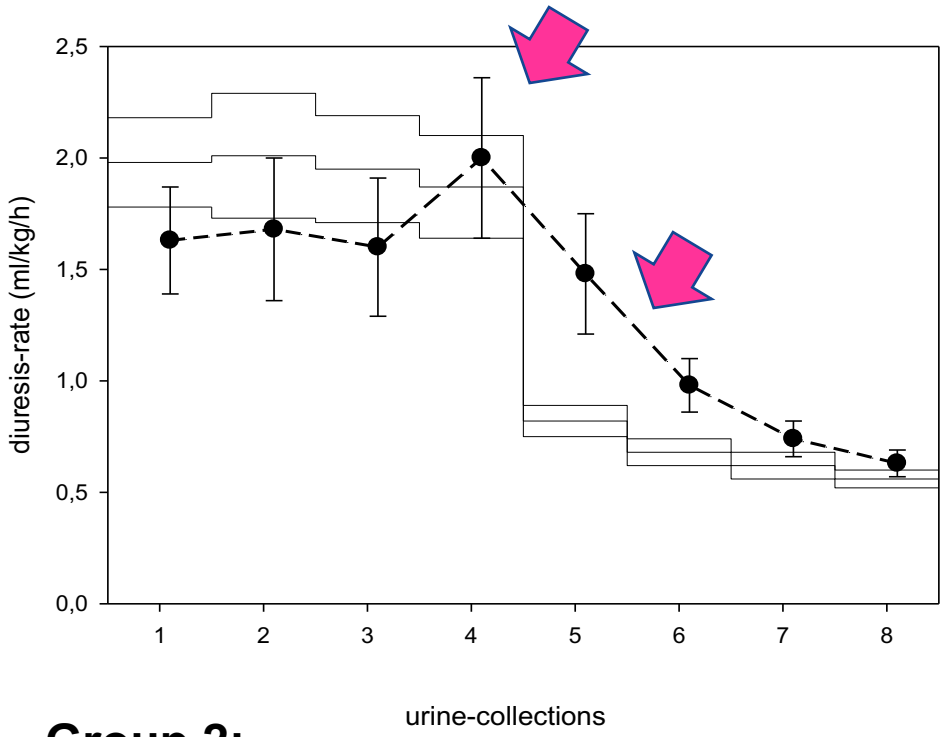
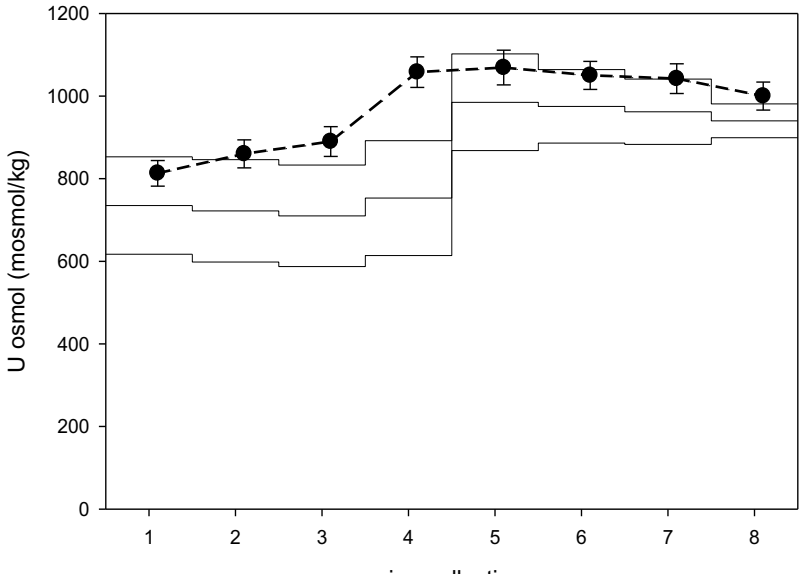


Fig3

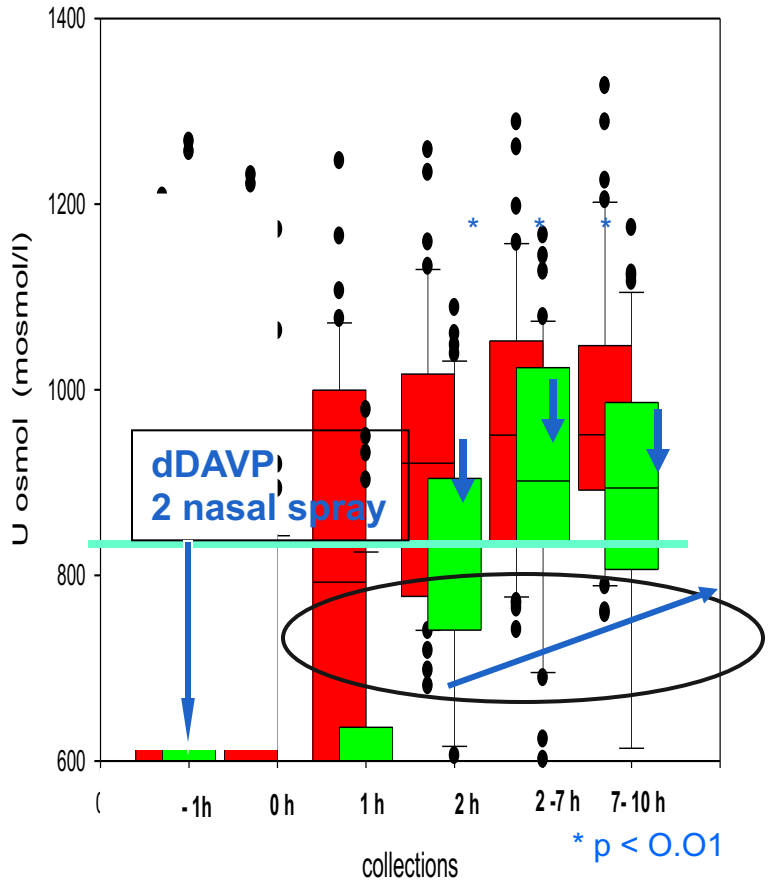


Group 2:
(high) Normal 24 h intake,
normal 24 h excretion
But high nocturnal excretion of osmol and water
high osmotic load in the evening

J.Dehoorne Desmopressin resistant nocturnal polyuria secundary to increased osmotic excretion J Urology 2006

Fluid load reduces desmopressin response

fig 2

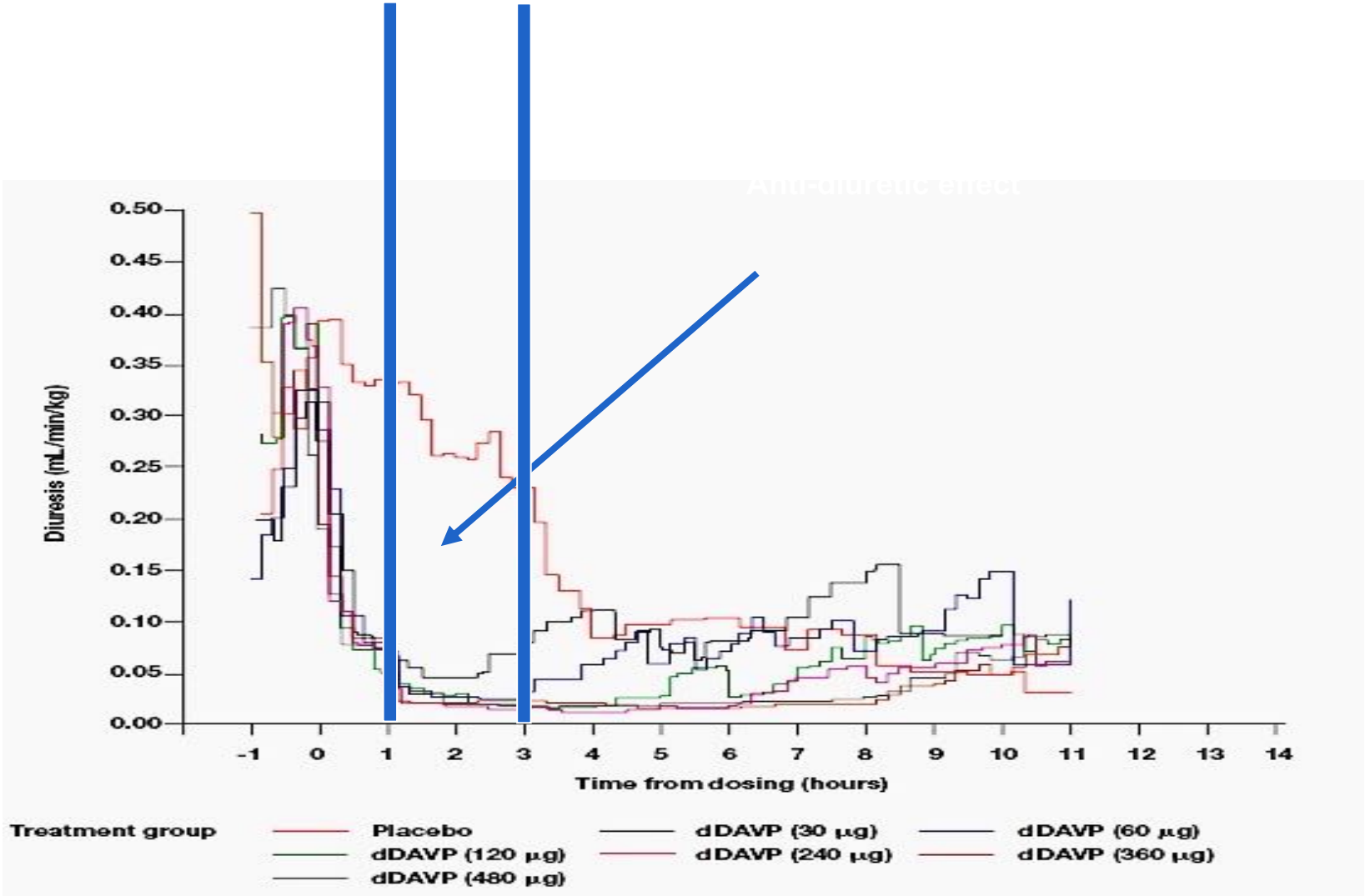


- 30% lower U osmol results
- in 30% higher diuresis-rate
- .. and bedwetting

EVIDENCE OF PARTIAL dDAVP RESPONSE RELATED TO POOR PHARMACODYNAMIC EFFECTS OF dDAVP NASAL SPRAY

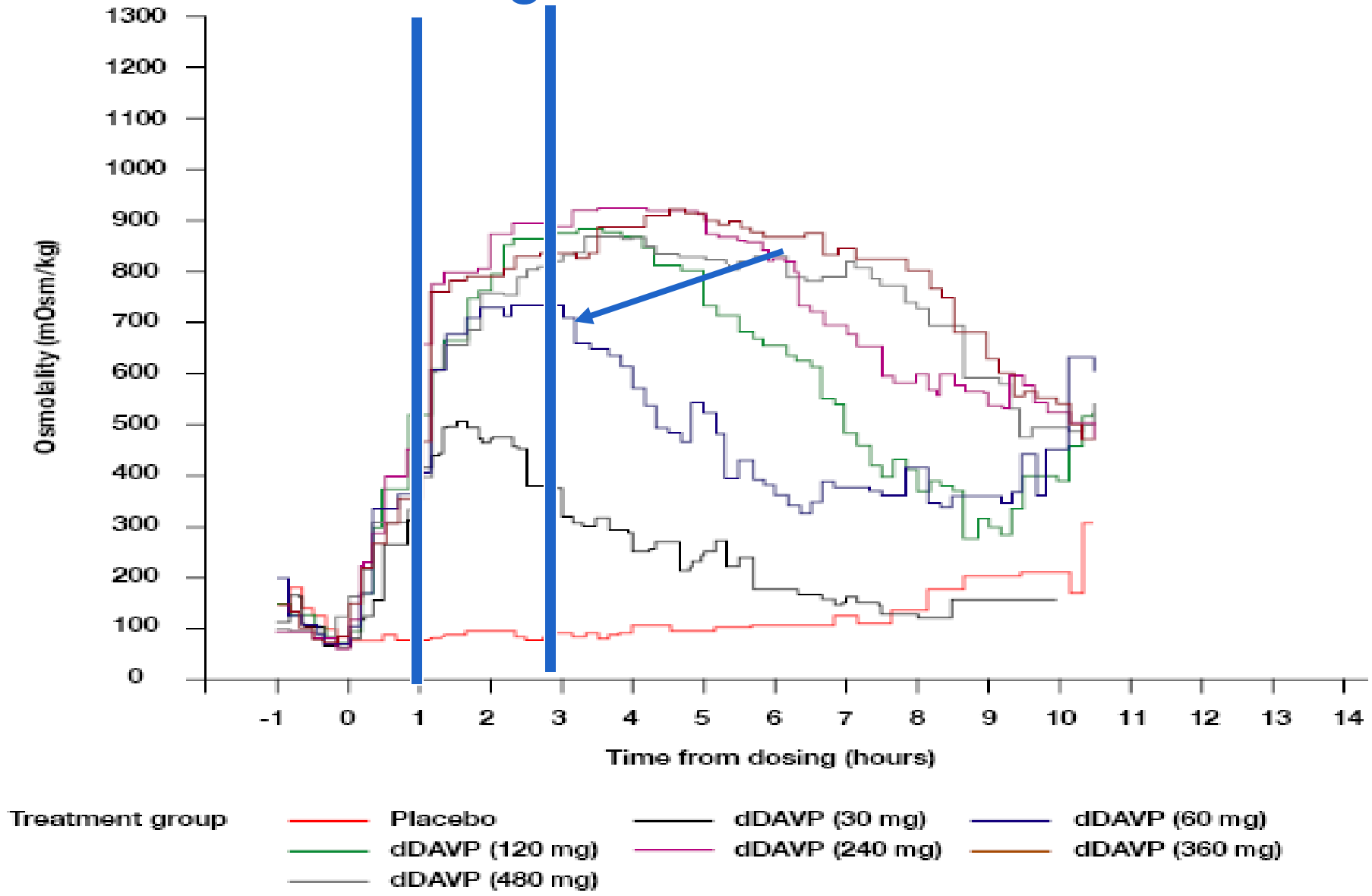
(De Guchtenaere J Urology,2009)

3. PK/PD: Timing administration melt



Vande Walle JG et al. BJU Int 2006;97(3):603–9

PK/PD: Timing administration



Pharmacodynamic studies of dDAVP melt during water-load Vande Walle JG et al. *BJU Int* 2006;97(3):603–9

Bladder Dysfunction:

1) Enuresis ?
2) Nocturia ?
3) LUTS ?
4) Bladder dysfunction in CAKUT en CKD?

Johan Vande Walle.
L Dossche

UZ GENT
UNIVERSITEIT GENT
SAFE PEDRUG

Safepedrug IWT 130033,
Frederik Paulson chair