W27: How Do I Manage LUTS in Patients with Cerebral Disorders?
Workshop Chair: Jalesh N. Panicker, United Kingdom
08 October 2015 14:30 - 16:00

<table>
<thead>
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<th>Start</th>
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<th>Topic</th>
<th>Speakers</th>
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</thead>
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<td>14:30</td>
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<td>Overview of LUTD in cerebral disorders</td>
<td>Jalesh N. Panicker</td>
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<td>14:45</td>
<td>15:05</td>
<td>Parkinson's Disease and Multiple System Atrophy (MSA)</td>
<td>Enrico Finazzi Agrò</td>
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<td>15:25</td>
<td>The dementias</td>
<td>Marcio Averbeck</td>
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<td>15:45</td>
<td>Stroke</td>
<td>Ryuji Sakakibara</td>
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<td>15:45</td>
<td>16:00</td>
<td>Discussion</td>
<td>All</td>
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</tbody>
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**Aims of course/workshop**
The aim of this workshop is to familiarise health care professionals with Lower Urinary Tract (LUT) dysfunction occurring in patients with common cerebral disorders and to review principles of management.

The objectives are:
1. To review the neurological basis for LUT dysfunction following cerebral disorders.
2. To explore the spectrum of LUT symptoms in common cerebral disorders, specifically Parkinson’s Disease and its’ mimics, the Dementias and Stroke.
3. To review strategies for management of LUT symptoms in these common cerebral disorders.

**Learning Objectives**
1. Understand why lower urinary tract symptoms occur in patients with cerebral disorders
2. Identify the patterns of lower urinary tract dysfunction that occur in patients with Parkinson’s Disease, dementia and stroke
3. Apply treatment strategies for managing incontinence in patients with cerebral disorders
What is Parkinson's disease?

Parkinson's disease (PD) is a degenerative disorder associated with loss of dopaminergic neurons, occurring around 1/1000 (LOE2). In addition to motor symptoms such as tremor, slow gait and easy fall, patients often show non-motor symptoms, including neuropsychiatric disorders, sleep disorders, sensory symptoms, and autonomic disorders (particularly OAB and constipation) (LOE2).

Parkinson Disease and LUTS

- Prevalence
  - 38-71%
  - 27-39%
- In both sexes
  - Higher prevalence of voiding phase LUTS in male pts.

Campos-Sousa RN: Arq Neuropsiquiatr 2003
Harvey: Am J Obstet Gynecol (2001)
**Parkinson Disease and LUTS**

- Most frequent symptoms
  - Nocturia
  - Urgency
  - Urgency Incontinence
  - Slow stream

*Siroky: Urol Clin N Am (2003)*

**Parkinson Disease and LUTS**

- Urodynamic patterns
  - Neurogenic detrusor overactivity
    - 67% of symptomatic pts
  - Detrusor underactivity
    - 8% of symptomatic pts
  - Normal detrusor function
    - 25% of symptomatic pts
  - D/S “dyssynergia”
    - 0–3%

*Siroky: Urol Clin N Am (2003); Wingo: Mov Dys 2006*

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**Sphincter Bradykinesia**

Sphincter Bradykinesia can be defined as the failure of the pelvic floor muscles and external urethral sphincter to relax rapidly before detrusor contraction (= manifestation of skeletal muscle rigidity in the pelvic floor)

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**PD and MSA**

- Multiple system atrophy (MSA) is a disease that simulates PD but is more progressive and leads to urinary retention (formerly called Shy-Drager syndrome).
- Approximately 50% of patients with MSA are initially misdiagnosed as having PD
- The incidence of MSA versus PD is approximately 1:10.

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**PD and MSA**

- MSA can present either as a poorly levodopa-responsive parkinsonism (MSA-P) or a cerebellar dysfunction (MSA-C); however, in either condition, additional bladder dysfunction causing urinary incontinence is an early feature.

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**PD and MSA**

- Discriminators for the differential diagnosis:
  - incomplete bladder emptying (PVR>100 ml)
  - open bladder neck at the start of bladder filling without accompanying DO (internal sphincter denervation)
  - change of sphincter EMG, which is rarely seen in patients with PD

- Urodynamics and neurologic evaluations are imperative in suspected PD patients if the response to anticholinergics is unsatisfactory incontinence is a problem, or when an indwelling catheter is needed.
Parkinson Disease and LUTS

Are symptoms due to comorbidity?

Comorbidities
- POP (women)
- BPH (men)
- Ageing
  - Gray, Age Ageing (1995)
- Prevalence not influenced by antiP drugs Sakakibara, Auton Neurosci (2001)

Parkinson Disease and LUTS

Symptoms due to PD
- In both sexes different urodynamic patterns and symptoms in comparison to non PD patients Silva, Urolology (2001); Malek, Int Urogynecol J Pelvic Floor Dysfunct. (1999)
- Correlation between LUTS severity and disability
  - Araki, J Neurol Neurosurg Psychiatr (2000)
  - Sammour, Urology (2009)
- Correlation between LUTS severity and dopaminergic function
  - Sakakibara, J Neurol Sci (2011)
- Improvement of LUTS during chronic L-DOPA treatment
  - Brosse, Neurology (2007)

CNS and Micturition control

The representation of bladder fullness by midbrain activity may therefore not be solely localized to the PAG, but instead may be a more diffuse activation encompassing other midbrain sites such as the substantia nigra...

Neurones located in substantia nigra and ventral tegmentum respond to bladder filling and help determine the biphasic micturition reflex. Our data suggest that midbrain involvement in micturition control extends beyond the PAG...

Alteration in brain activation sites in response to bladder filling may be related to the pathophysiology of detrusor overactivity in patients with Parkinson’s disease.

Parkinson Disease and LUTS

Role of basal ganglia on bladder function

- Improvement of LUTS during chronic L-DOPA treatment
  - Brosse, Neurology (2007)

Bladder Control Matrix

(CJ Fowler, 2005)
Role of Dopamine D1 – D2 Receptors on Micturition in animals

The different role of D1 and D2 dopamine receptors on lower urinary tract (LUT) behavior has been demonstrated in few animal studies.

Seki et al. (Neurourol Urodyn. 20(1):105-13, 2001)
D2 selective agonists and D1 selective antagonists reduction of the bladder capacity and of the volume threshold for the micturition reflex in conscious rats

Yoshimura et al (J Pharmacology and exper. therapeutics. 286; 228-233, 1998)
Similar experience in normal and MPTP parkinsonian monkeys

Central D2 stimulation worsens detrusor overactivity in PD pats

- LD alone worsened detrusor overactivity
- L-sulpiride (central and peripheral D2 antagonist) coadministration counteracted the worsening in a dose dependent manner. Domperidone (peripheral D2 antagonist) coadministration failed to determine the same counteraction.
- A central acute D2 stimulation seems to be responsible of a reduction of bladder capacity with worsening of detrusor overactivity in patients with mild PD.


Role of Dopamine D1 – D2 Receptors on Micturition

Hypothesis
D2 receptors  facilitation of micturition reflex
D1 receptors  tonic inhibition of bladder voiding

Parkinson Disease and LUTS

Anti-muscarinics

Non-subtype selective
- Atropine, hyoscyamine
- Propantheline
- Tolterodine
- Trospium

Subtype selective (M3)
- Darifenacin
- Solifenacin
**HEMATO-ENKEFALIC BARRIER**

- **Hematoma activity**
- **Media activity**
- **Neurotransmitter**
- **Electrode reaction**
- **Controlled**

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**NE and mCh receptors in bladder smooth muscle**

- **Cell membrane**
- **β3**
- **M2**
- **M3**
- **M4**
- **cAMP**
- **Ca2+**
- **IP3**
- **Relaxation**
- **Contraction**

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**β3 selectivity of mirabegron in relaxation of human bladder strips**

Mirabegron is a potent and selective β3-AR agonist.

Adapted from Takasu T et al. 2007 J Pharmacol Exp Ther 321(2):642–647.

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**Mirabegron: Mean number of incontinence episodes per 24 hrs - co-primary endpoint**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n=291)</th>
<th>Mirabegron 50mg (n=293)</th>
<th>Tolterodine ER 4mg (n=300)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>-1.17</td>
<td>-1.57</td>
<td>-1.27</td>
</tr>
<tr>
<td>Mean change in 24 hrs</td>
<td>-1.17</td>
<td>-1.57</td>
<td>-1.27</td>
</tr>
</tbody>
</table>

Statistically significant improvement versus placebo at the 0.05 level with multiplicity adjustments.

ns: No statistically significant improvement versus placebo.


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**ClinicalTrials.gov**

- A Phase II Study of Mirabegron and Botulinum Toxin A for the Treatment of Overactive Bladder in Parkinson's Disease (ClinicalTrials.gov Identifier: NCT01258020)."
Electrostimulations

**Percutaneous Tibial Nerve Stimulation**

![Image of Percutaneous Tibial Nerve Stimulation](image)

### Research Article

#### Percutaneous tibial nerve stimulation (PTNS) efficacy in the treatment of lower urinary tract dysfunctions: a systematic review

**Gabriele Cappelli, Luca Trappini, Valeria Merello, Alessandro Marmiroli, Angela D’Italia, Giovanni Conforti, and Giorgio Marmiroli**

**Date:** March 2015

**Purpose:** To evaluate the efficacy of percutaneous tibial nerve stimulation (PTNS) as a treatment for lower urinary tract dysfunction in adults with neurogenic bladder dysfunction.

**Methods:** A systematic review of randomized controlled trials (RCTs) was conducted to assess the efficacy of PTNS in the treatment of lower urinary tract dysfunction.

**Results:** A total of 12 RCTs were included in the review. PTNS was found to be effective in improving symptoms and quality of life in patients with neurogenic bladder dysfunction.

**Conclusion:** PTNS is an effective treatment for lower urinary tract dysfunction in patients with neurogenic bladder.

**References:**


### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Significant improvement in QoL</td>
<td>PTNS effective</td>
</tr>
<tr>
<td>Group B</td>
<td>No improvement</td>
<td>PTNS ineffective</td>
</tr>
</tbody>
</table>

**Note:** QoL = Quality of Life
DBS and LUTS

- Deep brain stimulation of subthalamic nucleus (STN-DBS)
  - Therapeutic option for severe patients
  - Improvement of neurological status
- LUTS?

Urodynamic improvement
- Cystometric capacity and reflex volume
  - Median 320 versus 130 ml, p = 0.04
- No effects on voiding

Chronic improvement of LUTS (DBS STN)
  - Winge K: Mov Disord. 2007

Repetitive Transcranial Magnetic Stimulation (rTMS)

- Repetitive magnetic stimulus at freq
  - > 1 Hz (high frequency)
  - < 1 Hz (low frequency)
- For pain, depression, neurorehabilitation

On motor cortex
- High frequency TMS => facilitatory effects
- Low frequency TMS => inhibitory effects

Sawyer HR, Rothwell J: Exp Brain Res. 2001
rTMS
- 2-week course of low frequency 1 Hz repetitive transcranial magnetic stimulation (rTMS)
- Increase of bladder capacity and the first sensation of filling
- Reduction of IPSS score

Surgery for BPH and PD
- Urodinamic evaluation
  - Obstruction
  - Differenzial diagnosis to MSA
    - Perineal EMG?
  - PD is not a contraindication to surgery
    - U: minimal %

Anti-Parkinson drugs and LUTS

Dopaminergic therapy and LUTS: contrasting evidence
- Kuno et al. Mov Disord 1997 Abstract
- Uchiyama et al. Mov Disord 2003; (18): 573-8

Acute L-dopa administration worsens detrusor overactivity in PD pats.
- Urodynamic session with a double examination: in the off treatment condition and 1 hour after acute challenge with carbidopa-dopa 50/200 mg
- The acute L-dopa challenge significantly worsened bladder overactivity and bladder capacity
Chronic L-dopa administration improve detrusor overactivity in PD pats.

- Chronic L-dopa monotherapy administered
- Two months later, second urodynamic session 1 hour after the acute carbidopa/L-dopa challenge
- Improvement in first sensation of bladder filling, detrusor overactivity and bladder capacity
- The acute and chronic L-dopa effects may be due to the different synaptic concentrations or to the activation of postsynaptic mechanisms obtained by chronic administration.

Stroke

Ryuji Sakakibara, MD, PhD
Neurology, Sakura Medical Center, Toho University, Sakura, Japan

**My topic**

To review a relationship between stroke & bladder

Prefrontal cortex briefly: PET & NIRS

Frontal stroke: urodynamics & MRI

Elderly white matter ischemia: a brain etiology of OAB

How to manage bladder disorder in stroke patients?

OAB & functional incontinence

**The frontal micturition center by PET**

Brain areas activated by urinary storage in healthy volunteers: H$_2$O-PET

Dasgupta, Kavia & Fowler BJU International 2007

**The frontal micturition center by NIRS**

The area activated was the bilateral lateral prefrontal area, particularly Brodmann’s areas 8, 10 and 46

24 degree room temperature, sitting, eyes closed, running water playing (white noise)
Frontal cortex and sphincter

[3H]proline injection study

a. Lateral view of South American Monkey (Saimiri) brain. The site and extent of injected [3H]proline are indicated by jet black. The dotted area indicates FC, fissura centralis.
b. Autoradiogram illustrating the projection from area 4 to the first sacral segment of the cord. The stippling depicts the pattern of silver grains indicating the course and termination of fibers.
Nakagawa 1980 Brain Res

Frontal cortex and sphincter
Sensory evoked potential and magnetoencephalogram

Electrical stimulation in the sacral skin elicited magnetic dipole in the sensory motor area.
Matsushita 2008

OAB: overactive bladder

"The length of a film should be directly related to the endurance of the human bladder." - Alfred Hitchcock.

"Yae" (eight layered) Cherry Blossom

Stroke: acute

- R internal carotid/middle cerebral artery occlusion
- Cere (acute phase)
- Left hemispheric neglect (subacute phase)
- Left hemiplegia, hemisensory decrease
- Urinary retention (acute phase: < 10% cases)
- OAB wet

Acute left hemianopia referred from an ophthalmologist
Stroke! → admitted

Question

1. Which is the main complaint of this lady?
2. Does she have motor paresis?
3. Does she have bladder disorder?
Bladder disorder in stroke

Within 3 months from onset
72; 67 male, 15 female
mean age 59 years
63 infarction, 9 hemorrhage

OAB is common

Bladder disorder relates with motor paresis

bladder disorder

severe moderate mild none

motor paresis

Bladder disorder in stroke

OAB is common

within acute phase

1996 JNS Sakakibara

Bladder dysfunction:

- often accompanied with hemiparesis
- not accompanied with sensory aphasia or hemianopsia

Urodynamic findings

Detrusor overactivity, detrusor-sphincter dyssynergia,
uninhibited sphincter relaxation

With bladder dysfunction

- medial frontal cortex (visible curve)
- basal ganglia
- brainstem

Without bladder dysfunction

- genu of internal capsule
- bladder

Urinary incontinence predicts poor outcome, why?

- Because:
  - 1) the same lesion might cause neurogenic bladder dysfunction (neurogenic UI), motor or cognitive impairment (functional UI), or (combined UI); these three are marked in severe, bilateral brain lesions. This further implies severe systemic atherosclerosis, including myocardial complications.
  - Night toileting may also cause falls.
  - UI may secondarily cause psychological depression and interfere with quality of life.

Cherry Blossoms in Maruyama Park, Kyoto
White matter ischemia in elderly: slow

- Recent MRI health surveys in general population with age>55 yrs revealed 'silent' white matter lesions (>grade3/9) in around 10% (7.6-24%)
- Increases with age & atherosclerotic risk factors (hypertension, eNOS/AT2R gene polymorphism etc.)

Symptomatology
(cerebro-) vascular dementia
vascular parkisonism
vascular incontinence (OAB)


Is OAB (brain etiology) related with cognitive??

- The inhibitory control or go-no-go paradigm can be assessed by: not tapping when examiner taps twice
- Inhibitory control task is decreased in WMD with DO.

Management of stroke: mostly life-style diseases

- Atherosclerotic risk factors
- Antiplatelet, antithrombotics

Cherry Blossoms in Stone Garden, Ryoanji temple, Kyoto
How to manage OAB in stroke patients?

OAB: bladder training
SUI: pelvic floor training
Nocturia: check bladder diary
Prostate: ultrasound > 20g
Anticholinergics:
- Choose ones not easily penetrating BBB to avoid cognitive changes
- α3-adrenergic agonist: Mirabegron can be a choice

Stroke & functional incontinence

- Alzheimer’s disease
- Dementia with Lewy bodies
- Basal ganglia injury
- Cognitive decline
- Loss of initiative
- Gait disturbance (parkinsonism)

- Detrusor overactivity (DO)
- Neurogenic bladder dysfunction, overactive bladder (OAB)
- Anticholinergic drugs (use with caution)

Take home message

- Prefrontal cortex is a key area to regulate micturition, which is commonly affected by stroke. In OAB patients, it is deactivated.
- Frontal stroke (acute) is common and causes OAB. Urodynamics often shows detrusor overactivity.
- White matter ischemia (slow) is common in elderly that causes OAB.
- Anticholinergics and a β3 agonist are a choice for treating OAB in stroke patients. Functional incontinence often overlaps, which needs a particular care.
HOW DO I MANAGE LUTS IN PATIENTS WITH DEMENTIA?

Márcio Augusto Averbeck, MD, MSc

TOPICS

- Types of Dementia
- Why is important for the physician to know the different types of dementia?
- Causes of LUTS in dementia patients
- Conclusions and take-home messages

TYPES OF DEMENTIA

Alzheimer’s Dementia
- Alzheimer’s disease (AD) is the most common form of dementia (50%)

Vascular Dementia
- It is the second most common form of dementia (20%)

Dementia with Lewy Bodies (DLB)
- It is the third most common form of dementia (3.5 per 100,000 person-years) (~10%)

Normal Pressure Hydrocephalus (NPH)
- Prevalence ~ 3%


TOPICS

- Types of Dementia
- Why is important for the physician to know the different types of dementia?
- Causes of LUTS in dementia patients
- Conclusions and take-home messages

TYPES OF DEMENTIA

Alzheimer’s Dementia
- Alzheimer’s disease (AD) is the most common form of dementia (50%)

- Early symptom = short memory loss
- Later = long-term memory loss, confusion, irritability, aggression, mood swings, trouble with language
- No cure

Types of dementia

Alzheimer's Dementia
- Alzheimer's disease (AD) is the most common form of dementia (50%)

Vascular Dementia
- It is the second most common form of dementia (20%)
  - Caused by problems in the blood supply to the brain, typically by a series of minor strokes.
  - Cognitive impairment after one or many cerebrovascular events.
  - Early detection and accurate diagnosis are important, as vascular dementia is at least partially preventable.

Dementia with Lewy Bodies (DLB)
- It is the third most common form of dementia (~10%)
  - Lewy bodies are abnormal proteins deposits within neurons (clumps of alpha-synuclein and ubiquitin proteins, which are detectable in post mortem brain histology).
  - Rapid onset and progression.
  - Its primary feature is cognitive decline, which can lead to hallucinations.

Normal Pressure Hydrocephalus (NPH)
- Prevalence ~ 3%
  - Caused by decreased absorption of cerebrospinal fluid.
  - Typical symptoms: gait disturbance, urinary incontinence, and dementia.
  - This is the only type of dementia that is potentially reversible (shunt surgery).

Why is important for the urologist to know the different types of dementia?

1. Because the occurrence of LUTS during the course of the disease is different
2. The type of LUTS and, therefore, the urological management are distinct too

Prevalence of Urinary Incontinence in Patients with or without Dementia

TOPICS

- Types of Dementia
- Why is important for the physician to know the different types of dementia?
- Causes of LUTS in dementia patients
- Conclusions and take-home messages
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- Types of Dementia
- Why is important for the physician to know the different types of dementia?
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CAUSES OF LUTS IN DEMENTIA PATIENTS

1. Neurological disease itself
2. Neurological pharmacotherapy
3. Comorbidities

CAUSES OF LUTS IN DEMENTIA PATIENTS

1. Neurological disease itself
2. Neurological pharmacotherapy
3. Comorbidities

ALZHEIMER'S DISEASE

• In Alzheimer's disease (ALD), the prevalence of UI (usually unawareness urinary incontinence) ranges from 23% to 48% and the onset of incontinence usually occurs in late-stage dementia. (LE 3)
• Behavioural therapy strategies, including toilet training and prompted voiding, are especially useful and should be started earlier enough to induce reflex behaviour, which can be used later, when dementia progresses (going to the toilet = micturition/defecation; glass of water = drinking). (LE 5/GR C*)
• Antimuscarics may enhance behaviour therapy, especially when the bladder capacity is reduced. (LE 5/GR C*)


OBJECTIVE:
The present study sought to investigate lower urinary tract symptoms and urodynamic and cystometric findings in Parkinson disease (PD), dementia with Lewy bodies (DLB), and Alzheimer disease (AD).

CONCLUSIONS:
Urgency and urge incontinence suggest detrusor overactivity, which was more prevalent in dementia with Lewy bodies than in Parkinson disease and Alzheimer disease, whereas mean voided volume, free flow, cystometric bladder capacity, and detrusor pressure were similar in the groups. Frequency of micturition could not be reliably assessed in patients with dementia.

Ransmayr GN, Holliger S, Schletterer K, Heidler H, Deibl M, Poewe W, Madersbacher H, Kiss G.
**URODYNAMIC FINDINGS**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Cystometric Capacity</th>
<th>pDetr. max.</th>
<th>Detrusor Overactivity</th>
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<tbody>
<tr>
<td>LBD</td>
<td>12</td>
<td>254 ± 185</td>
<td>38.5 ± 33.7</td>
<td>11 ± 92%</td>
</tr>
<tr>
<td>PD</td>
<td>13</td>
<td>256 ± 76</td>
<td>42.2 ± 19.4</td>
<td>6 ± 46%</td>
</tr>
<tr>
<td>AD</td>
<td>10</td>
<td>297 ± 154</td>
<td>45.8 ± 21.5</td>
<td>4 ± 40%</td>
</tr>
<tr>
<td>p</td>
<td>0.97</td>
<td>0.21</td>
<td>0.02</td>
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</table>

Ransmayr et al. 2008

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**TYPE OF DEMENTIA AND LUTS**

**VASCULAR DEMENTIA**

Pathophysiology of LUTD
Loss of bladder filling sensation
Urinary incontinence

*with detrusor overactivity in 45%
*with detrusor underactivity in 55%

Neurological symptoms: cognitive deficits, disorientation, motor restrictions

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**TYPE OF DEMENTIA AND LUTS**

**NPH**

- LUTS have been reported in up to 93% of the patients with idiopathic Normal Pressure Hydrocephalus (NPH), in which the most frequent symptoms were urgency (64%), frequency (64%) and UI (57%).
- NPH (as well as vascular dementia) manifests with gait disturbance, dementia and UI.
- Symptoms of NPH may be reversed by shunt surgery (such as ventriculo-peritoneostomy).
  However, UI and dementia are two-fold less likely to improve than gait disturbance. (Le 2)

PHARMACOTHERAPY FOR DEMENTIA

• First-line treatment: cholinesterase-inhibitors
• Second-line treatment: memantine

• Cholinesterase-Inhibitors* and memantine are given by the neurologist to increase acetylcholine activity in the brain by stimulation M1 receptors

But Cholinesterase-Inhibitors may also be effective in the periphery, thus inducing/increasing urge-incontinence.

Deterioration of continence may be misinterpreted as disease progression and antimuscarinics are therefore given to this patients.

*Donepezil - Arizept®, Rivastigmine - Exelon®, Galantamine - Reminyl®
* Memantine - Namenda®

OAB and memory disorders increase

Decline in delayed memory recall relative to age 20–29 (%)

Frequency of first-time use of medication for urinary incontinence in men and women in different age groups

With vs Without Dementia

PHARMACOTHERAPY FOR DEMENTIA

The Dilemma with Antimuscarinics in OAB Patients treated with Cholinesterase-Inhibitors for Cognitive Impairment

• Cholinesterase-inhibitors are given by the neurologist to improve memory
• Antimuscarinics are given by the urologist to improve urgency

Antimuscarinics crossing the blood-brain barrier (BBB) are bound to the M1 receptors, and block them for acetylcholine. Thus, rapid (2-3 days) deterioration of cognition (delirium, hallucinations) can occur.

CAUSES OF LUTS IN DEMENTIA PATIENTS

1. Neurological disease itself
2. Neurological pharmacotherapy
3. Comorbidities

Reports of 3 relevant publications:

“Cholinesterase inhibitor treatment was associated with significant worsening of urinary continence.”

“...approximately 7% risk of precipitating urinary incontinence and current incontinence may be significantly worsened.”
Gill, Arch InternMed, 2005

“There was no significant difference between Rivastigmine and Donepezil.”
Hashimoto, Lancet, 2000
• LUT problems in patients with dementia are not necessarily related to the neurologic pathology
• Other diseases such as prostate pathology and pelvic organ prolapse might also have an influence

• Clinical assessment including history, clinical examination, urine analysis, bladder diary, free flowmetry and PVR should be as comprehensive as possible (LE 5/GR A*)

• Types of Dementia
• Why is important for the physician to know the different types of dementia?
• Causes of LUTS in dementia patients
• Conclusions and take-home messages

CONCLUSIONS

• Overall, urinary incontinence (UI) affects around 50% of men and 60% of women with dementia (LE 3)
• Onset, characteristics and etiology of LUTS vary according to the type of dementia, effects of neurological pharmacotherapy and comorbidities. (LE 3)

TAKE-HOME MESSAGES

1. Various forms of dementia cause different LUTS at different times during disease process and therefore require individualized treatment strategies.
2. Despite of the type of dementia, the treatment of LUTS should be tailored to individual patient needs and disease status, taking into account factors like mobility, cognitive function and general medical condition. (LE 3/4, GR C)
3. Conservative management includes prompted voiding, toilet training and oral antimuscarinics. (LE 3/4, GR C)

TAKE-HOME MESSAGES

4. In Alzheimer's patients, "Unawareness Urinary Incontinence" occurs later in the disease process. Treatment of choice are behavioral interventions, especially the toilet training. Antimuscarinics may increase bladder capacity and can thus facilitate the training measures.
5. In Lewy-bodies dementia, symptoms of overactive bladder and urinary incontinence occur early during the course of disease. Antimuscarinics play an important role in the treatment of LUTS in these patients.
6. In vascular dementia detrusor underactivity is more common than in other forms of dementia, and may require an specific therapy (intermittent catheterization?).
7. Physicians should consider the potential risk of coprescribing cholinesterase inhibitors + antimuscarinics to patients with dementia. (LE 4, GR B⁴)
8. Be careful in treating OAB with antimuscarinics (consider CNS side effects) and detect cognitive changes. (LE 3/4, GR B⁴)
9. For the treatment of OAB symptoms antimuscarinics which cause as little cognitive side effects should be preferred. Oral oxybutynin should be avoided.
10. Aggressive therapy of incontinence must be reserved for patients with good general status and ambulation. (LE 4, GR C)

11. In the late stages of disease, incontinence aids/products may be essential. An indwelling catheter should be avoided if possible.
Overview of lower urinary tract dysfunction in cerebral disorders

Jalesh N. Panicker MD, DM, FRCP
Consultant Neurologist in Urology
The National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology
Queen Square, London

ICSworkshopMontrealOct2015

Stroke
Parkinson’s Disease
Tumours
Trauma
Dementias

Spinal
Multiple Sclerosis
Trauma
Tumour

Sacral / Infrasacral
Disc prolapse
Tumour
Pelvic nerve injury
Small fibre neuropathy

Clinical course: Stable conditions

Disability

Time

Clinical course: Progressive conditions

Disability

Time
**Suprapontine**
- Stroke
- Parkinson’s Disease
- Tumours
- Trauma
- Dementias

**Spinal**
- Multiple Sclerosis
- Trauma
- Tumour

**Sacral / Infrasacral**
- Disc prolapse
- Tumour
- Pelvic nerve injury
- Small fibre neuropathy

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**Neuropsychiatric changes contributing to incontinence**

- Impaired initiation
- Limited coping mechanisms
- Impaired awareness for bladder sensation or incontinence

---

**Stroke**

**Parkinson’s Disease**

**Tumours**

**Trauma**

**Dementias**

**Multiple Sclerosis**

**Trauma**

**Tumour**

**Disc prolapse**

**Pelvic nerve injury**

**Small fibre neuropathy**

**• Storage symptoms**
- PVR: < 100mL
- Detrusor overactivity

**• Storage / voiding symptoms**
- PVR: usually elevated
- Detrusor overactivity, detrusor sphincter dyssynergia

**• Predominantly voiding symptoms**
- PVR: elevated
- Often acontractile detrusor

---

**Incontinence: is it always due to an overactive bladder?**

- Overactivity
- Stress incontinence
- Overflow

**Functional: Mobility, toilet access**

- Cognitive impairment: visuospatial disorientation, memory, aphasia, compulsive behaviour, social inhibition, apraxia

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**Neurogenic bladder**

- Diabetes mellitus
- Obstructive sleep apnea syndrome
- Cardiac failure
- The ageing bladder
- Medications: diuretics, ChEI

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**Neurogenic bladder dysfunction**

- Cerebral disorder: eg. stroke, dementia, PD
- Cognitive and behavioural changes
- Neurogenic bladder dysfunction
- Functional incontinence
- Urological causes
- Cholinesterase inhibitors

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**Nucleus basalis projects to the neocortex**

**PPN projects to the thalamus**

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**Obstructive sleep apnea**

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**Lower urinary tract symptoms**

**Antimuscarinics**

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**Antimuscarinics**
First line treatment: Antimuscarinics

- Oxybutynin
- Pranetheline
- Darifenacin
- Propiverine
- Solifenacin
- Trospium
- Tolterodine
- Feostardine

Which one?

The “anticholinergic burden”

- High >15 pmol/L
  - Amitriptyline
  - Doxepin
  - Clozapine
  - Atropine
  - Dicyclamine

- Moderate 5 – 15pmol/L
  - Nortriptyline
  - Paroxetine
  - Chlorpromazine
  - Olanzapine
  - Oxybutynin

- Mild 0.5 – 5 pmol/L
  - Citalopram
  - Escitalopram
  - Fluoxetine
  - Mirtazapine
  - Quetiapine
  - Temazepam
  - Ranitidine

- Adapted from Gerretsen P, Pollock BG Drugs Ageing 2011
- Slide courtesy Adrian Wagg

Anticholinergic burden (ACB) scale

- Score > 3 clinically relevant

Excerpt from patient’s letter 2.2015

I am sorry to bother you, but as a patient on Detrasitol, I am worried about the bad press with regard to the medication increasing the risk of dementia. I would very much appreciate your professional opinion as to whether I should change my medication. At
Active efflux across the blood brain barrier

- Active transport mechanism: permeability-glycoprotein (P-gp)
- Lower levels than would be expected for its lipophilicity
- Trospium, Darifenacin, Fesoterodine

Selective Muscarinic receptor binding: M3 versus M1 receptor

<table>
<thead>
<tr>
<th>Agent</th>
<th>Formulation</th>
<th>Dosage</th>
<th>Dose</th>
<th>Chemical Structure</th>
<th>Muscarinic M3/M1</th>
<th>M2/M4, M5, Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darifenacin</td>
<td>Extended release</td>
<td>Twice daily</td>
<td>3, 4 mg</td>
<td>Quaternary amine</td>
<td>0.9</td>
<td></td>
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<tr>
<td>Tolerodine</td>
<td>Extended release</td>
<td>Once daily</td>
<td>1.2 mg</td>
<td>Parasympathomimetic</td>
<td>0.6</td>
<td></td>
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<tr>
<td>Oxybutynin</td>
<td>Extended release</td>
<td>Once daily</td>
<td>30 mg</td>
<td>Parasympathomimetic</td>
<td>0.6</td>
<td></td>
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<tr>
<td>Fesoterodine</td>
<td>Extended release</td>
<td>Once daily</td>
<td>2.4 mg</td>
<td>Parasympathomimetic</td>
<td>0.6</td>
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</tr>
<tr>
<td>Trospium</td>
<td>Extended release</td>
<td>Twice daily</td>
<td>25 mg</td>
<td>Quaternary amine</td>
<td>1.5</td>
<td></td>
</tr>
</tbody>
</table>

Trospium chloride