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

Start	End	Topic	Speakers
14:30	14:45	Overview of LUTD in cerebral disorders	Jalesh N. Panicker
14:45	15:05	Parkinson's Disease and Multiple System Atrophy (MSA)	Enrico Finazzi Agrò
15:05	15:25	The dementias	Marcio Averbeck
15:25	15:45	Stroke	Ryuji Sakakibara
15:45	16:00	Discussion	All

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

Parkinson's Disease and MSA

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Unit of Functional Urology
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Tor Vergata University
S. Lucia Rehabilitation Hospital
Rome, ITALY

MANAGEMENT OF BLADDER DYSFUNCTION IN PARKINSON'S DISEASE AND OTHER GAIT DISORDERS

Neurourology and Urodynamics

A Guideline for the Management of Bladder Dysfunction in Parkinson's Disease and Other Gait Disorders

Ryuji Sakakibara,[1]* Jalesh Panicker,[2] Enrico Finazzi-Agro,[3] Valerio Iacovelli,[4] Homero Bruschini,[5] and The Parkinson's Disease Subcommittee, The Neurourology Promotion Committee in The International Continence Society
[1]Neurology, Internal Medicine, Sakura Medical Center, Toho University, Sakura, Japan
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[3]Department of Experimental Medicine and Surgery, Tor Vergata University and Unit for Functional Urology, Policlinico Tor Vergata University Hospital, Rome, Italy
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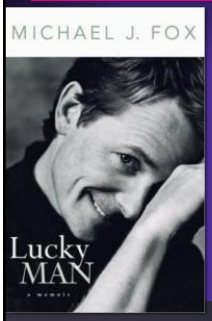
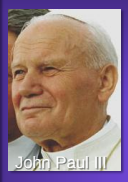
[5]Urology, University of Sao Paulo, Brazil

What is Parkinson's disease?




John Paul III


Muhammad Ali at
1996 Atlanta Olympic Game

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%

Siroky: Urol Clin N Am (2003)

  - 27-39%

Campos-Sousa RN: Arq Neuropsiquiatr 2003

- In both sexes
  - Higher prevalence of voiding phase LUTS in male pts.

Harvey: Am J Obstet Gynecol (2001)

Parkinson Disease and LUTS

- LUTS: Lower urinary tract symptoms
  - Filling phase
    - 55% of symptomatic pts
  - Voiding phase
    - 11% of symptomatic pts
  - Mixed
    - 34% of symptomatic pts

Siroky: Urol Clin N Am (2003)

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); Winge: Mov Dys 2006

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)

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.

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.

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?

Parkinson Disease and LUTS

- Comordibities
  - POP (women)
  - BPH (men)
  - Higher prevalence of void. phase LUTS in male pts.
    Harvey: Am J Obstet Gynecol (2001)
  - Ageing
    Gray: Age Ageing (1995)
  - Prevalence not influenced by antiP drugs
    Sakakibara: Auton Neurosci (2001)

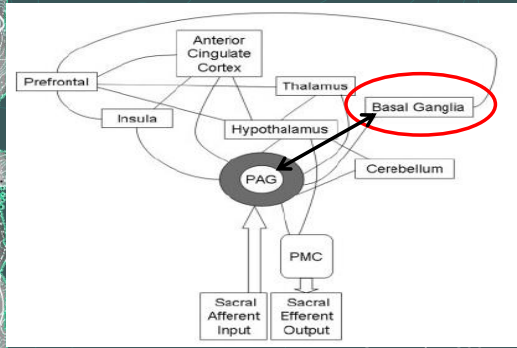
Parkinson Disease and LUTS

- Symptoms due to PD
  - In both sexes different urodynamic patterns and symptoms in comparison to non PD patients
    Defreitas: Urology. (2003); Myers: Int Urogynecol J Pelvic Floor Dysfunct. (1999)
  - Correlation between LUTS severity and disability
    Araki: J Neurol Neurosurg Psichiatry (2000)
    Sammour ZM: Neurourol Urodyn (2009)
  - Correlation between LUTS severity and dopaminergic function
    Sakakibara: J Neurol Sci (2001)
  - Improvement of LUTS during chronic L-DOPA treatment
    Brusa: Neurology (2007)

Parkinson Disease and LUTS

Role of basal ganglia on bladder function

Bladder Control Matrix



CJ Fowler, 2005

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.
  Dasgupta R…, Fowler CJ: J Urol. 2005
- Significant brain activation during detrusor overactivity was found in the periaqueductal gray, supplementary motor area, cerebellar vermis, insula, putamen and thalamus…
- 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.
  Kitta T et al: J Urol. 2006

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

Role of Dopamine D1 – D2 Receptors on Micturition

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

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.
- Brusa L, Petta F, Pisani A, Miano R, Stanzione P, Moschella V, Galati S, Finazzi Agrò E: Central acute D2 stimulation worsens bladder function in patients with mild Parkinson's disease. J Urol. 2006 Jan;175(1):202-6

Parkinson Disease and LUTS

Therapy

NDO

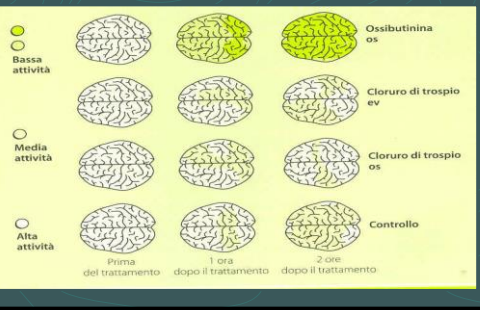
Antimuscarinics

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

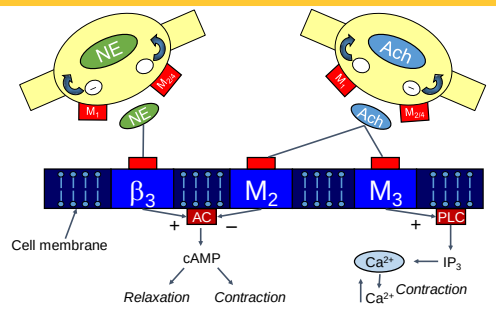
Subtype selective (M_3)
- Darifenacin
- Solifenacin


Atropa belladonna

HEMATO-ENKEFALIC BARRIER

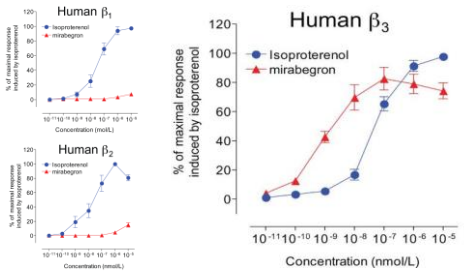


NE and mAch receptors in bladder smooth muscle



Chapple CR. Urology. 2000;55:33–46

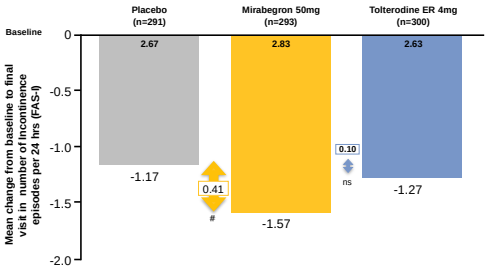
β_3 selectivity of mirabegron in relaxation of human bladder strips



Mirabegron is a potent and selective β_3-AR agonist

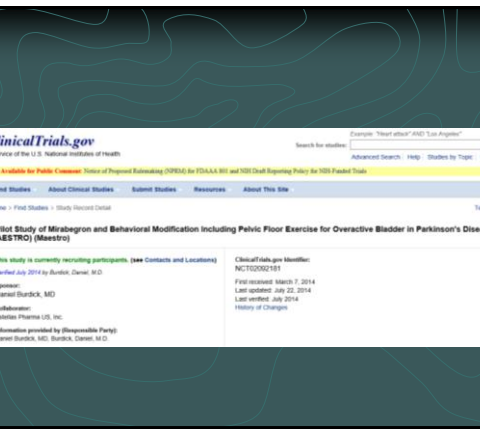
Adapted from Takasu T et al. 2007 J Pharmacol Exp Ther 321(2):642–647

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

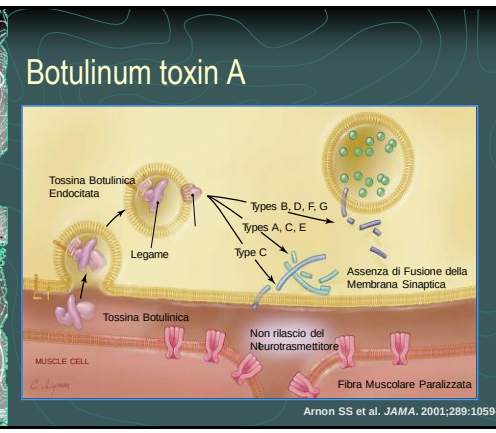


#Statistically significant improvement versus placebo at the 0.05 level with multiplicity adjustments
ns: No statistically significant improvement versus placebo

Adapted from Khullar V, et al. Eur Urol 2013; 63: 283–95



Botulinum toxin A



Arnon SS et al. *JAMA*. 2001;289:1059-70.

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PubMed.gov US National Library of Medicine National Institutes of Health

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Display Settings: Abstract

Send to:

J Urol. 2011 Sep;186(3):960-4. doi: 10.1016/j.juro.2011.04.071. Epub 2011 Jul 24.

Botulinum toxin type A in patients with Parkinson's disease and refractory overactive bladder.

Giannantoni A, Conte A, Proietti S, Giovannozzi S, Rossi A, Fabbrini G, Porena M, Berardelli A.

Department of Urology and Andrology, Ospedale S. Maria della Misericordia, and Department of Neurology, University of Perugia, Perugia, Italy. agianton@libero.it

Abstract

PURPOSE: In this 6-month followup study we investigated the effect of intradetrusor injection of 100 U botulinum toxin type A in patients with Parkinson's disease and refractory detrusor overactivity.

MATERIALS AND METHODS: Eight patients with Parkinson's disease and detrusor overactivity refractory to anticholinergics were injected with 100 U botulinum toxin type A. Daytime and nighttime urinary frequency, and urinary incontinence episodes were recorded. Patients also completed a standardized quality of life questionnaire on incontinence and a visual analog scale on the impact of bladder problems on daily life activities, and underwent urodynamic assessment, including pressure flow studies. Clinical and urodynamic assessment was performed before, and 1, 3 and 6 months after injection.

RESULTS: In all patients 100 U botulinum toxin type A induced decreased daytime and nighttime urinary frequency, a decreased number of urinary incontinence episodes, increased quality of life scores and, as shown by increased maximum cystometric capacity, improved urodynamic findings. In 2 patients with Parkinson's disease post-void residual urine volume developed.

CONCLUSIONS: Intradetrusor injection of 100 U botulinum toxin type A induced clinical and urodynamic improvement in overactive bladder symptoms that lasted at least 6 months in patients with Parkinson's disease.

PMID: 21791351 [PubMed - indexed for MEDLINE]

Display Settings: Abstract

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Urology. 2014 Jan;83(1):22-7. doi: 10.1016/j.urology.2013.09.017. Epub 2013 Nov 11.

OnabotulinumtoxinA office treatment for neurogenic bladder incontinence in Parkinson's disease.

Anderson RU[1], Orenberg EK[2], Glowa P[2].

Author information

[1]Department of Urology, Stanford University School of Medicine, Stanford, CA. Electronic address: rua@stanford.edu.
[2]Department of Urology, Stanford University School of Medicine, Stanford, CA.

Abstract

OBJECTIVE: To evaluate safety and effectiveness of low-dose (100 U) onabotulinumtoxinA (onabotA) bladder injections as an office procedure with topical anesthesia only for patients with Parkinson's disease (PD) and incontinence.

METHODS: Qualified patients who failed oral antimuscarinic agents participated in an open-label study. They discontinued antimuscarinics, provided a King's Health Questionnaire (KHQ), voiding symptom score, and 3-day voiding diary. Free uroflowmetry with post-void ultrasounds and cystometrogram pressure/flow studies were performed. Patients underwent flexible cystoscopy and injections of onabotA 100 U (10 U/mL) dispersed into 10-20 submucosal/detrusor sites of the bladder, including the trigone. Voiding diaries, questionnaires, and free uroflowmetry with post-void ultrasound residual urine measurements were repeated after 1, 3, and 6 months.

RESULTS: Twelve men and 8 women were treated: mean age, 70.4 years; duration of disease, 10.6 years; median bladder contraction volume, 115 mL; maximum bladder pressure, 62 cm; and post-void volume, 9 mL. Moderate to marked symptom relief at 3 months and a 50% incontinence decrease over 6 months relative to pretreatment was reported in 59% patients ($P \leq .02$); 5 patients failed to complete the 6-month endpoint. No urinary retention required catheterization.

CONCLUSION: Office cystoscopy with low-dose onabotA injection treatment is a potential long-term management strategy for patients with PD and urinary incontinence who fail oral antimuscarinic agents. The treatment seems to be safely utilized for older men with BPH as well as women with potential hypoactive detrusor function.

PMID: 24231202 [PubMed - indexed for MEDLINE]

Electrostimulations

Percutaneous Tibial Nerve Stimulation

Gaziev et al. BMC Urology 2013, 13:61
http://www.biomedcentral.com/1471-2490/13/61

BMC Urology

RESEARCH ARTICLE Open Access

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

Gabriele Gaziev[1], Luca Topazio[1], Valerio Iacovelli[1], Anastasios Asimakopoulos[1], Angelo Di Santo[1], Cosimo De Nunzio[2] and Enrico Finazzi-Agrò[1,3]*

Table 5 Results of the use of PTNS in Patients affected by neurogenic bladder

Authors	Years	Control group	PNT			RCT	Methods	Level	Results	Female (%)	Mean age	Multicenter
			n	Positive	%							
Kabay S	2009 [29,39,41]	N/A	32	15	47	N	Urodynamic	2-3	50% improvement cystometric capacity	41	64 (44–78)	N
Gobbi C	2011 [40]	N/A	21	16	76	N	Clinical	2-3	Patient perception of Bladder Cond	76	46 (29–62)	N
Kabay S	2009 [29,39,41]	N/A	19	19	100	N	Urodynamic		Custometry parameters	100		N

J Wound Ostomy Continence Nurs. 2015 Jan-Feb;42(1):94-9. doi: 10.1097/WON.0000000000000078.

Transcutaneous tibial nerve stimulation in the treatment of lower urinary tract symptoms and its impact on health-related quality of life in patients with Parkinson disease: a randomized controlled trial.

Pantuzzello MC[1], D'Ancona CA, Lucio A, Campos RM, Abreu A.

Author information

Abstract

PURPOSE: A randomized controlled trial study was performed to evaluate the efficacy of transcutaneous tibial nerve stimulation (TTNS) and sham TTNS, in patients with Parkinson disease (PD) with lower urinary tract symptoms (LUTS).

DESIGN: Randomized controlled trial.

SUBJECTS AND SETTINGS: Thirteen patients with a diagnosis of PD and bothersome LUTS were randomly allocated to one of the following groups: Group I: TTNS group (n = 8) and group II: Sham group (n = 5). Both groups attended twice a week during 5 weeks; each session lasted 30 minutes.

METHODS: Eight patients received TTNS treatment and 5 subjects allocated to group II were managed with sham surface electrodes that delivered no electrical stimulation. Assessments were performed before and after the treatment; they included a 3-day bladder diary, Overactive Bladder Questionnaire (OAB-V8), and the International Consultation on Incontinence Quality of Life Questionnaire Short Form (ICIQ-SF), and urodynamic evaluation.

RESULTS: Following 5 weeks of treatment, patients allocated to TTNS demonstrated statistically significant reductions in the number of urgency episodes ($P = .004$) and reductions in nocturia episodes ($P < .01$). Participants allocated to active treatment also showed better results after treatment in the OAB-V8 and ICIQ-SF scores ($P < .01$, respectively). Urodynamic testing revealed that patients in the active treatment group showed improvements in intravesical volume at strong desire to void ($P < .05$) and volume at urgency ($P < .01$) when compared to subjects in the sham treatment group.

CONCLUSION: These findings suggest that TTNS is effective in the treatment of LUTS in patients with PD, reducing urgency and nocturia episodes and improving urodynamic parameters as well as symptom scores measured by the OAB-V8 and health-related quality-of-life scores measured by the ICIQ-SF.

PMID: 25549314 [PubMed - in process]

DBS and LUTS

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

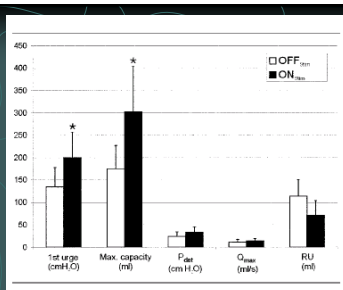


Fig. Comparison of the urodynamic filling and micturition parameters with deep brain stimulation of the subthalamic nucleus (STN-DBS) switched on and switched off ($p < 0.005$*). RU = residual urine.*

Seif C: Ann Neurol. 2004 Jan;55(1):118-20.

DBS and LUTS

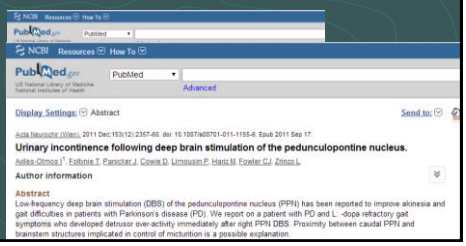
- Urodynamic improvement
  - Cystometric capacity and reflex volume
    - (median 320 versus 130 ml., p = 0.043 250 versus 110, p = 0.04).
- No effects on voiding

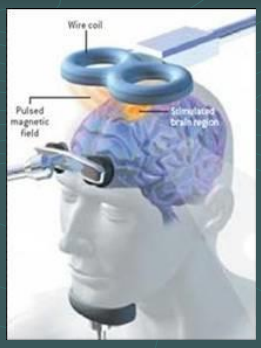
Finazzi-Agro E: J Urol. 2003 Apr;169(4):1388-91.

DBS and LUTS

- Chronic improvement of LUTS (DBS STN)

Winge K: Mov Disord. 2007





Repetitive Transcranial Magnetic Stimulation (rTMS)

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

Lefaucheur JP: Suppl Clin Neurophysiol. 2004
Liepert J: Acta Neurochir Suppl. 2005
Simons W:World J Biol Psychiatry. 2005

- On motor cortex
  - High frequency rTMS ⇨ facilitatory effects
  - Low frequency rTMS ⇨ inhibitory effects

Siebner HR, Rothwell J: Exp Brain Res. 2003

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

Effects of Inhibitory rTMS on Bladder Function in Parkinson's Disease Patients

Livia Brusa, MD, PhD,[1] Enrico Finazzi Agrò, MD,[2] Filomena Petta, MD,[2] Francesco Sciobica, MD,[2] Sara Torriero, MD,[3] Emanuele Lo Gerfo, MD,[3] Cesare Iani, MD,[1] Paolo Stanzione, MD,[3,4*] and Giacomo Koch, MD[3,4]

[1]UOC Neurologia, Ospedale S. Eugenio, Rome; [2]Clinica Urologica, Università di Roma Tor Vergata, Rome; [3]Fondazione Santa Lucia IRCCS, Rome; [4]Clinica Neurologica, Dipartimento di Neuroscienze, Università di Roma Tor Vergata, Rome, Italy

Abstract: **Patients affected by Parkinson's disease (PD) may present with lower urinary tract (LUT) dysfunction characterized by involuntary detrusor overactivity. We evaluated possible impact of a 2-week course of low frequency 1 Hz repetitive transcranial magnetic stimulation (rTMS) on LUT behavior in eight advanced PD patients complaining of urinary disturbances. We tested the effects of rTMS measuring urodynamic examination and the International Prostate Symptoms Score (IPSS) questionnaire, used for evaluation of subjective LUTS. rTMS was able to improve temporarily LUT behavior in PD patients, increasing bladder capacity and the first sensation of filling phase. Moreover, a reduction of IPSS score was noticed, due to an improvement on filling phase symptoms. The beneficial effects assessed with the IPSS lasted for up to 2 weeks after the end of the stimulation. rTMS seems to be an effective, noninvasive alternative treatment for PD patients with urinary disturbances.**

Surgery for BPH and PD

Surgery for BPH and PD

- Urodinamic evaluation
  - Obstruction
  - Differenzial diagnosis to MSA
    - Perineal EMG?
- PD is not a contraindication to surgery
  - Up to 70% of success
  - UI: minimal %

Fowler C: Funct. Neurol. 2001; Roth B: J Urol 2009

Anti-Parkinson drugs and LUTS

Dopaminergic therapy and LUTS: contrasting evidence

Fitzmaurice *HJ Br J Urol* 1985; 57:652.
Christmas TJ et al. The Lancet 1988; 24/31: 1451-53.
Aranda B et al. Neurol Urodynam. 1993; 12: 203-9.
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.

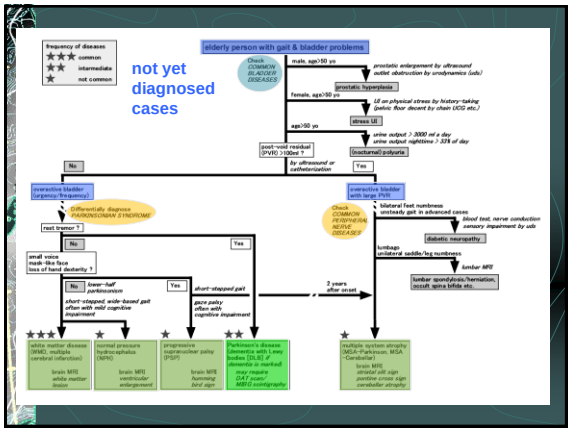
- Urodynamic session with a double examination: in the off treatment condition and 1 hour after acute challenge with carbidopa/l-dopa 50/200 mg
- The acute l-dopa challenge significantly worsened bladder overactivity and bladder capacity

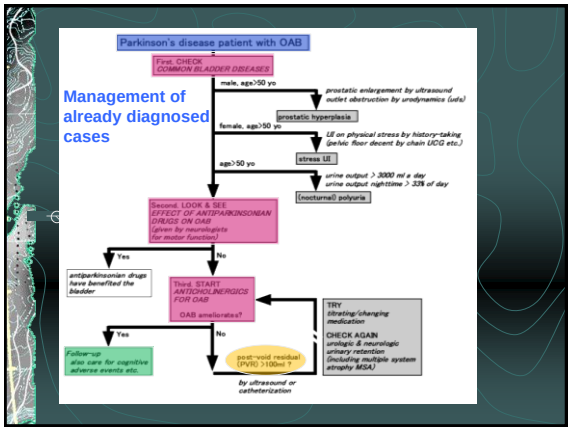
Brusa L, Petta F, Pisani A, Moschella V, Iani C, Stanzione P, Miano R, Finazzi-Agrò E. Acute vs chronic effects of l-dopa on bladder function in patients with mild Parkinson disease. Neurology. 2007 May 1;68(18):1455-9.

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.

Brusa L, Petta F, Pisani A, Moschella V, Iani C, Stanzione P, Miano R, Finazzi-Agrò E. Acute vs chronic effects of l-dopa on bladder function in patients with mild Parkinson disease. Neurology. 2007 May 1;68(18):1455-9.





Sakura Medical Center, Sakura, Japan

ICS2015 Montreal
W27 How Do I manage LUTS in Patients with Cerebral Disorders?

Toho Sakura Neurology

Stroke

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

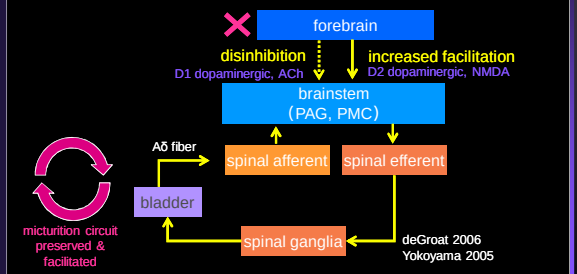
Toho University, Sakura Medical Center, Sakura, Japan
Toho Sakura Neurology
SAKURA: CHERRY BLOSSOM

My topic

Toho Sakura Neurology

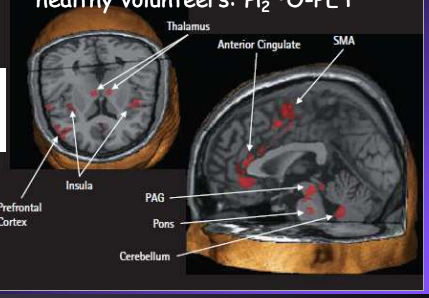
To review a relationship between stroke & bladder
Prefrontal cortex briefly : PET & NIRS
Frontal stroke : urodynamics & MRI
Elderly white matter ischemia : a brain etiology of OAB
How to manage bladder disorder in stroke patients ? : OAB & functional incontinence

Detrusor overactivity after forebrain lesion



The frontal micturition center by PET

brain areas activated by urinary storage in healthy volunteers: $H_2{}^{15}O$-PET



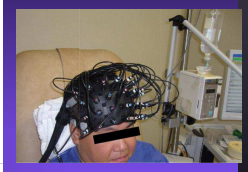
PFC, medial FC and deep structures are activated.

Dasgupta, Kavia & Fowler BJU Interantional 2007

UCL

The frontal micturition center by NIRS

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

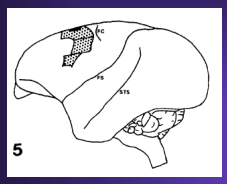


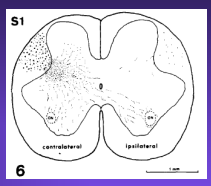
24 degree room temperature, sitting, eyes closed, running water playing (white noise)

Sakakibara R.
Neurourol Urodynam 2010.

Frontal cortex and sphincter

[3H]proline injection study

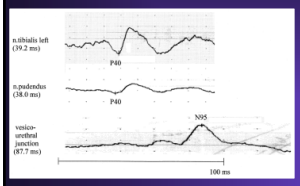




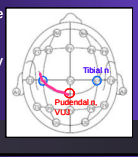
a. Lateral view of South American Monkey (Saimiri) brain. The site and extent of injected [3H]proline are indicated by jet black. The dotted area indicates area 4. FC, fissura centralis.
b. Autoradiogram illustrating the projection from area 4 to the first sacral segment of the cord. The stippling depicts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

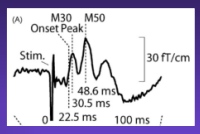
Frontal cortex and sphincter

Sensory evoked potential and magnetoencephalogram



Electrical stimulation in the dorsal penile nerve/ vesicourethral junction elicited SEP in the sensory motor area.
Nakagawa 1998





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

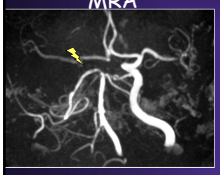
'Yae' (eight layered) Cherry Blossom

OAB: overactive bladder

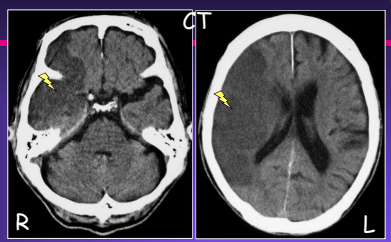
"The length of a film should be directly related to the endurance of the human bladder." - Alfred Hitchcock.

Stroke: acute

MRA



CT

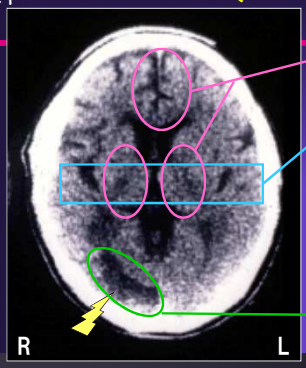


- R internal carotid/middle cerebral artery occlusion

- Coma (acute phase)
- Left hemispacial neglect (subacute phase)
- Left hemiplegia, hemisensory decrease
- all cause functional incontinence
- Urinary retention (acute phase, < 10% cases)
- OAB wet

Question

CT



Overactive bladder
(retention in acute phase)

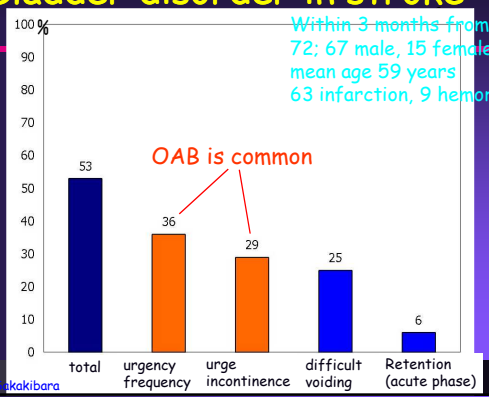
motor paresis

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

Acute left hemianopia referred from an ophthalmologist

Stroke! →admitted

Bladder disorder in stroke

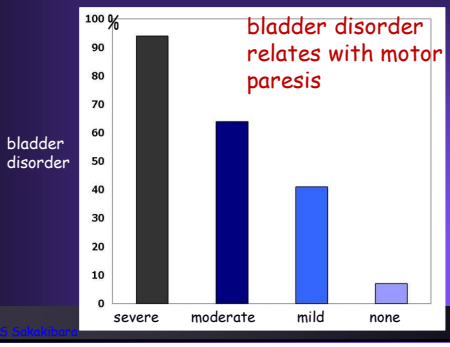


Within 3 months from onset
72; 67 male, 15 female
mean age 59 years
63 infarction, 9 hemorrhage

OAB is common

1996 JNS Sakakibara

Bladder disorder in stroke



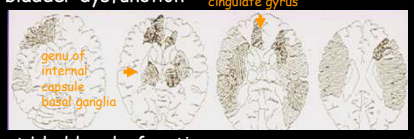
bladder disorder relates with motor paresis

1996 JNS Sakakibara

Bladder disorder in stroke

with bladder dysfunction

medial frontal cortex
cingulate gyrus



CT and MRI
stroke N=72

Bladder dysfunction: often accompanied with hemiparesis

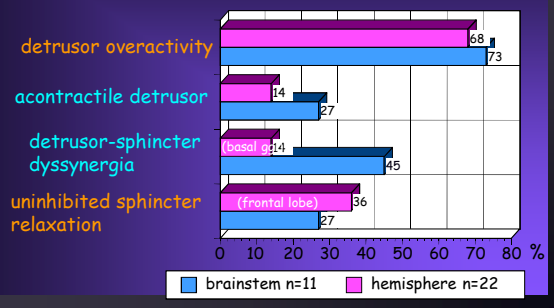
without bladder dysfunction

Bladder dysfunction: not accompanied with sensory aphasia or hemianopsia

1996 JNS Sakakibara et al.

Bladder disorder in stroke

Urodynamic findings

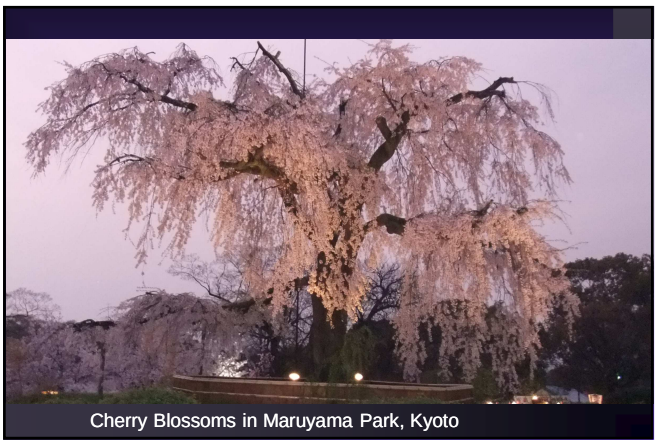


1996 JNS Sakakibara et al.

Bladder disorder in stroke

Urinary incontinence predicts poor outcome, why?

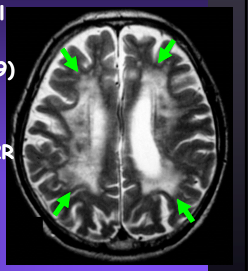
- Because:
- 1) the same lesion might cause neurogenic **bladder** dysfunction (neurogenic UI), **motor or cognitive** impairment (functional UI), or (combined UI); these three are marked in severe, bilateral brain lesions. This further implies severe systemic atherosclerosis, including myocardial complications.
- 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

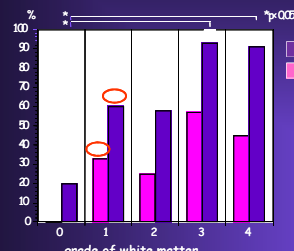
- Recent **MRI health surveys** in general population with age>55 yrs revealed 'silent' white matter lesions (>grade3/9) in around **10%** (7.6-24%)
- increases with age & atherosclerotic risk factors (hypertension, eNOS/AT2R gene polymorphism etc.)



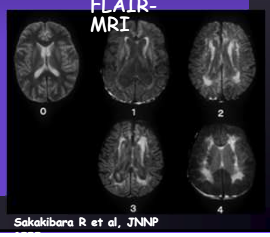
Symptomatology
(cerebro-) vascular dementia
vascular parkisonism
vascular incontinence (OAB)

Sakakibara , Panicker et al. Int J Urol 2014

Frequency of OAB in WMD



N=63

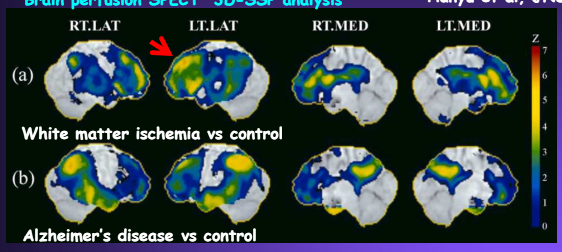


OAB increases with the grade of white matter lesions. OAB also appears earlier than gait & cognitive problems.

Sakakibara R et al, JNNP

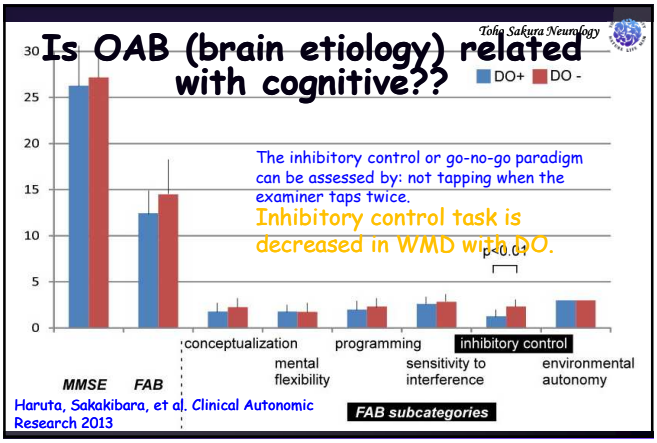
Brain perfusion between WMD and AD

Brain perfusion SPECT 3D-SSP analysis — Hanyu et al, JNS



In AD, parietal-temporal hypo-perfusion is common whereas in WMD, frontal hypo-perfusion is common.

Is OAB (brain etiology) related with cognitive??

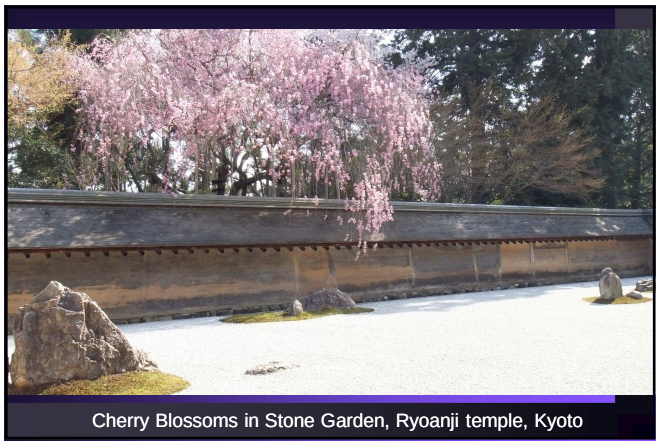


The inhibitory control or go-no-go paradigm can be assessed by: not tapping when the examiner taps twice.

Inhibitory control task is decreased in WMD with DO.

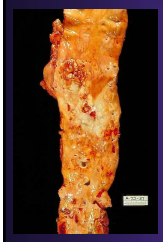
Haruta, Sakakibara, et al. Clinical Autonomic Research 2013

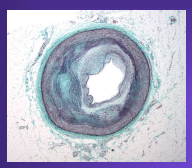
FAB subcategories



Cherry Blossoms in Stone Garden, Ryoanji temple, Kyoto

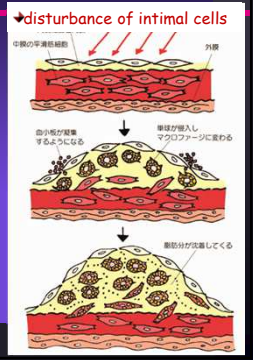
Management of stroke: mostly life-style diseases





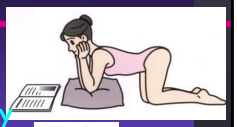
- Atherosclerotic risk factors
- Antiplatelet, antithrombotics

- disturbance of intimal cells



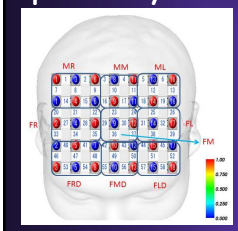
How to manage OAB in stroke patients?

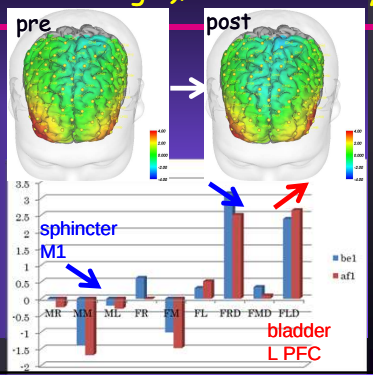
OAB: bladder training
SUI: pelvic floor training
noct.polyuria: check bladder diary
prostate: ultrasound > 20g
anticholinergics:
choose ones not easily penetrating BBB to avoid cognitive changes
β3-adrenergic agonist:
mirabegron can be a choice



Elderly OAB patients before/after fesoterodine (anticholinergic); a NIRS study

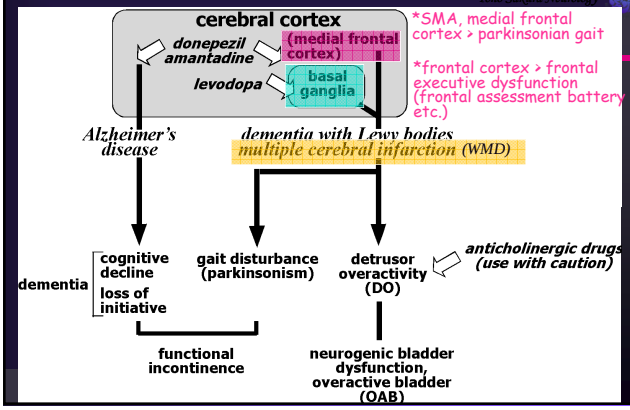
probe array





Between start & first sensation

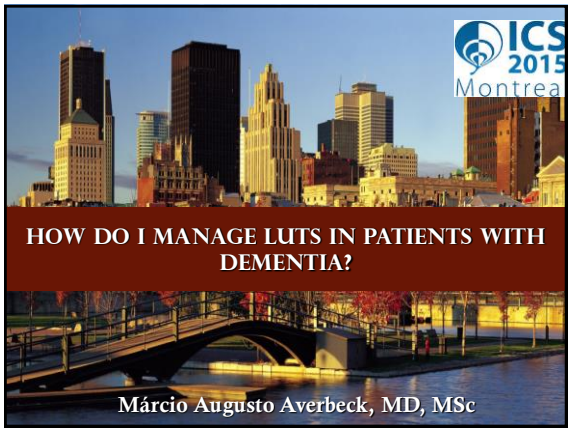
Stroke & functional incontinence



Cherry Blossoms on the water

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.



Márcio A. Averbeck, MD, MsC

Urologist
ICS Neurourology Promotion Committee
EAU/EUSP Clinical Fellowship – Innsbruck/Austria

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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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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%

Berchtold NC, Cotman CW. Evolution in the Conceptualization of Dementia and Alzheimer's Disease: Greco-Roman Period to the 1960s. Neurobiology of Aging. 1998;19(3):173–89.

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, agression, mood swings, trouble with language
- No cure

Berchtold NC, Cotman CW. Evolution in the Conceptualization of Dementia and Alzheimer's Disease: Greco-Roman Period to the 1960s. Neurobiology of Aging. 1998;19(3):173–89.

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.

Berchtold NC, Cotman CW. Evolution in the Conceptualization of Dementia and Alzheimer's Disease: Greco-Roman Period to the 1960s. Neurobiology of Aging. 1998;19(3):173–89.

TYPES OF DEMENTIA

- Lewy bodies are abnormal proteins deposits within neurons (clumps of 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.

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)

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Berchtold NC, Cotman CW. Evolution in the Conceptualization of Dementia and Alzheimer's Disease: Greco-Roman Period to the 1960s. Neurobiology of Aging. 1998;19(3):173–89.

TYPES OF DEMENTIA

- 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).

Normal Pressure Hydrocephalus (NPH)

•Prevalence ~ 3%

Berchtold NC, Cotman CW. Evolution in the Conceptualization of Dementia and Alzheimer's Disease: Greco-Roman Period to the 1960s. Neurobiology of Aging. 1998;19(3):173–89.

TOPICS

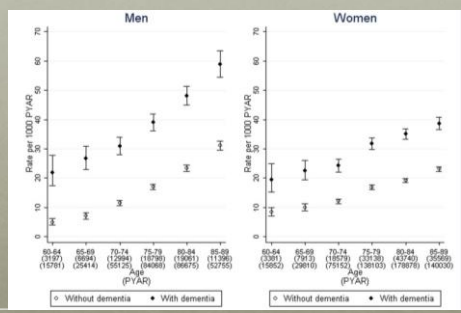
- Types of Dementia
- **Why is important for the physician to know the different types of dementia?**
- Causes of LUTS in dementia patients
- Conclusions and take-home messages

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

Ransmayr GN, Holliger S, Schletterer K, Heidler H, Deibl M, Poewe W. et al.: Lower Urinary Tract Symptoms in Dementia with Lewy Bodies, Parkinson disease, and Alzheimer Disease. J. Neurology 2008: 70:299-303
Savica R, Grossardt BR, Bower JH, Boeve BF, Ahlskog J, Rocca WA. Incidence of Dementia With Lewy Bodies and Parkinson Disease Dementia. JAMA Neurol. 2013
Berchtold NC, Cotman CW. Evolution in the Conceptualization of Dementia and Alzheimer's Disease: Greco-Roman Period to the 1960s. Neurobiology of Aging. 1998;19(3):173–89.

Prevalence of Urinary Incontinence in Patients with or without Dementia



Grant et al., PLoS Med. 2013 Aug;10(8):e1001505. doi: 10.1371/journal.pmed.1001505.
First diagnosis and management of incontinence in older people with and without dementia in primary care: a cohort study using The Health Improvement Network primary care database.

TOPICS

- Types of Dementia
- Why is important for the physician to know the different types of dementia?
- **Causes of LUTS in dementia patients**
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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

TYPE OF DEMENTIA AND LUTS

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*)**

Ransmayr GN, Holliger S, Schletterer K, Heidler H, Deibl M, Poewe W. et al.: Lower Urinary Tract Symptoms in Dementia with Lewy Bodies, Parkinson disease, and Alzheimer Disease. J. Neurology 2008: 70:299-303
Cacabelos R, Rodríguez B, Carrera C, Caamaño J, Beyer K, Lao JI, Sellers MA . APOE-related frequency of cognitive and noncognitive symptoms in dementia. Methods Find Exp Clin Pharmacol 1996; 18(10):693-706.

TYPE OF DEMENTIA AND LUTS

Lewy Bodies Dementia

•In contrast to Alzheimer's dementia, **LUTS usually occur earlier during the course of the disease or can even precede severe mental failure in Lewy Bodies Dementia** (LBD). **(LE 3)**

•Symptoms of overactive bladder (OAB) and detrusor overactivity are more common in LBD (and in vascular dementia), than in patients with ALD. **(LE 3)**

•The symptoms and urodynamics are useful for differential diagnosis, and are therefore helpful for the physician **(LE 3/GR C*)**

Sakakibara R, et al. J Neurol Neurosurg Psychiatry 2005; 76:729–732.
Ransmayr GN, Holliger S, Schletterer K, Heidler H, Deibl M, Poewe W. et al.: Lower Urinary Tract Symptoms in Dementia with Lewy Bodies, Parkinson disease, and Alzheimer Disease. J. Neurology 2008: 70:299-303

Neurology. 2008 Jan 22;70(4):299-303

LOWER URINARY TRACT SYMPTOMS IN DEMENTIA WITH LEWY BODIES, PARKINSON DISEASE, AND ALZHEIMER DISEASE.

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

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 pressor were similar in the groups. Frequency of micturition could not be reliably assessed in patients with dementia.

Micturition charts

	n	MF (24h)	mean micturition volume	urgency episodes n/24h	Incontinence-episodes (n/24h)
LBD	15 8,2	7,9 ± 3,4		198 ± 79	14,1
PD	15 3,8	6,4 ± 1,5		196 ± 53	7,7
AD	16 2,3	5,9 ± 1,6		165 ± 71	3,3
p *[KW ANOVA (p), x2 ...]*		0,34	0,48	<0,001	0,04

Ransmayr et al. 2008

URODYNAMIC FINDINGS

	n	Cystometric Capacity	pDetr. max.	Detrusor Overactivity
LBD	12	254 ± 185	38,5 ± 33,7	11 = 92%
PD	13	256 ± 76	42,2 ± 19,4	6 = 46%
AD	10	297 ± 154	45,8 ± 21,5	4 = 40%
p		0,97	0,21	0,02

Ransmayr et al. 2008

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

TYPE OF DEMENTIA AND LUTS

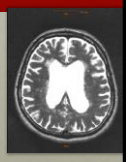
VASCULAR DEMENTIA

Therapy

- Toilet training
- Antimuscarinics
- Improvement of mobility (Physiotherapy)
- Intermittent catheterization if residual urine> 50% of the functional bladder capacity due to detrusor underactivity (arbitrary threshold)

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 twofold less likely to improve than gait disturbance. **(LE 2)**

Sakakibara R. Neurourol. Urodynam. 27:507–510. 2008.
McGirt MJ, et al. Neurosurgery. 2008 Feb;62 Suppl 2:670-7.

CAUSES OF LUTS IN DEMENTIA PATIENTS

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

PHARMACOTHERAPY FOR DEMENTIA

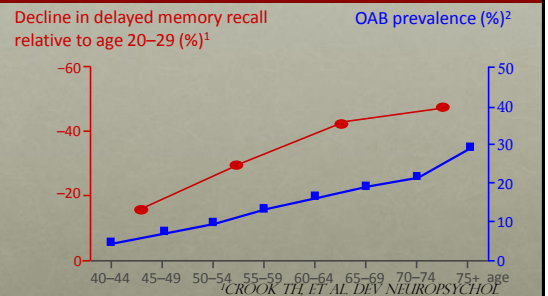
- **First-line treatment: cholinesterase-inhibitors**
- **Second-line treatment: memantine**

- 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®

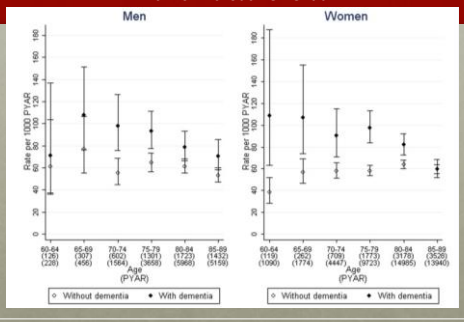
NICE technology appraisal guidance 217
guidance.nice.org.uk/ta217

OAB and memory disorders increase



[1]CROOK TH, ET AL. DEV NEUROPSYCHOL 1993;9:103–13
[2]MILSOM I, ET AL. BJU INT 2001;87:760–6

Frequency of first-time use of medication for urinary incontinence in men and women in different age groups With vs Without Dementia



Grant et al., PLoS Med. 2013 Aug;10(8):e1001505. doi: 10.1371/journal.pmed.1001505.
First diagnosis and management of incontinence in older people with and without dementia in primary care: a cohort study using The Health Improvement Network primary care database.

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.

PHARMACOTHERAPY FOR DEMENTIA

Reports of 3 relevant publications:

"Cholinesterase inhibitor treatment was associated with significant worsening of urinary continence."
Starr, J Am Ger Soc, 2007

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

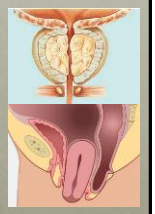
"There was no significant difference between Rivastigmine and Donepezil."
Hashimoto, Lancet, 2000

CAUSES OF LUTS IN DEMENTIA PATIENTS

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

COMORBIDITIES

- LUT problems in patients with dementia are not necessarely 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*)**



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**

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?).

TAKE-HOME MESSAGES

7. Physicians should consider the potential risk of coprescribing cholinesterase inhibitors + antimuscarinics to patients with dementia. **(LE 4, GR B*)**
8. Be careful in treating OAB with antimuscarinics (consider CNS side effects) and detect cognitive changes. **(LE 3/4, GR B*)**
9. For the treatment of OAB symptoms antimuscarinics which cause as little cognitive side effects should be preferred. Oral oxybutynin should be avoided.

TAKE-HOME MESSAGES

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.

THANK YOU !

Overview of lower urinary tract dysfunction in cerebral disorders

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Consultant Neurologist in Uroneurology
The National Hospital for Neurology and Neurosurgery
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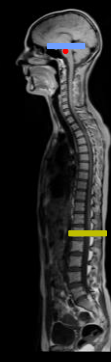
Queen Square, London

ICSworkshopMontrealOct2015

Suprapontine
- Stroke
- Parkinson's Disease
- Tumours
- Trauma
- Dementias

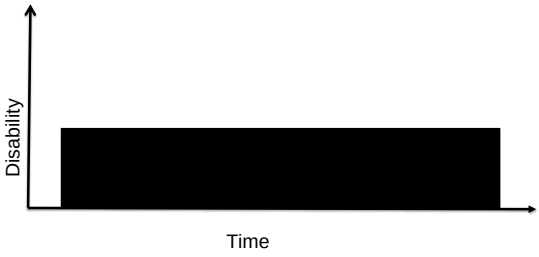
Spinal
- Multiple Sclerosis
- Trauma
- Tumour

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



UCL

Clinical course: Stable conditions



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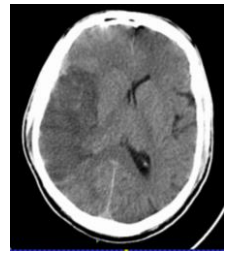
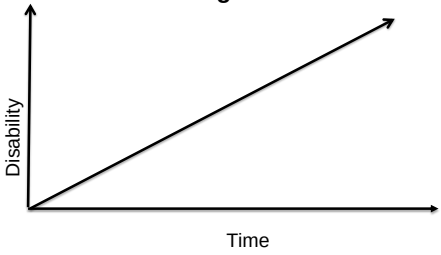


UCL

Clinical course: Progressive conditions



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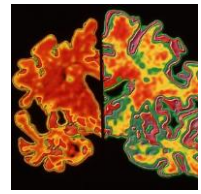

Suprapontine
Stroke
Parkinson's Disease
Tumours
Trauma
Dementias

Spinal
Multiple Sclerosis
Trauma
Tumour

Sacral / Infrasacral
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Tumour
Pelvic nerve injury
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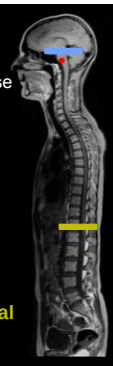
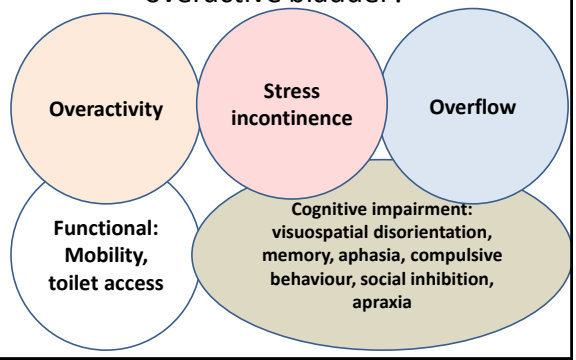


•Storage symptoms
•PVR: < 100mL
•Detrusor overactivity

•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?



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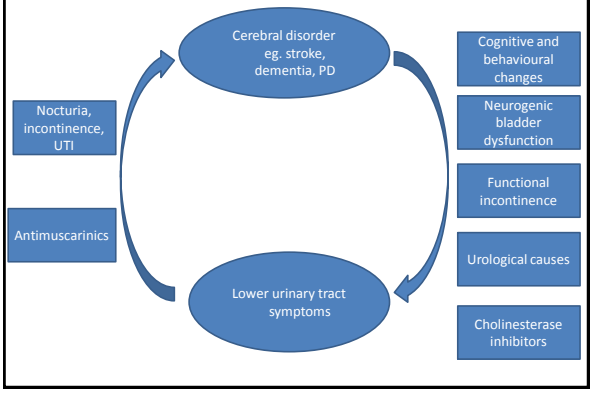
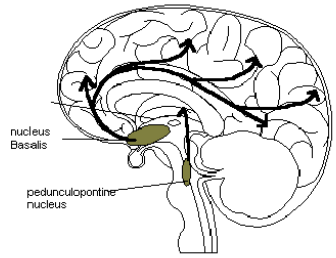
Neurogenic bladder
Local urological causes- bladder outlet obstruction, stress incontinence
Diabetes mellitus
congestive cardiac failure
Concomitant neurological disease eg. cervical spondylosis and myelopathy
Obstructive sleep apnea syndrome
The ageing bladder
Pedal oedema
medications: diuretics, ChEI

Neuropsychiatric changes contributing to incontinence

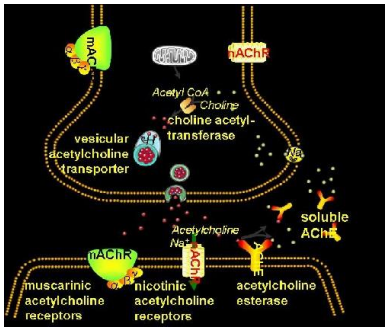
- Impaired initiation
- Limited coping mechanisms
- Impaired awareness for bladder sensation or incontinence



major cholinergic projections



Nucleus basalis projects to the neocortex
PPN projects to the thalamus



First line treatment: Antimuscarinics

Oxybutynin

Tolterodine

Trospium

Which one?

Propiverine

Propantheline

patch

Darifenacin

Solifenacin

Fesoterodine

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The "anticholinergic burden"

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

Moderate 5 – 15pmol/L
Nortriptyline
Paroxetine
Chlorpromazine
Olanzapine
oxybutynin

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

Slide courtesy Adrian Wagg

Adapted from Gerretsen P, Pollock BG Drugs Ageing 2011

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ACB Score 1 (mild)	ACB Score 2 (moderate)	ACB Score 3 (severe)
Alimemazine	Amantadine	Amitriptyline
Alprazolam	Belladonna alkaloids	Amoxapine
Alverine	Carbamazepine	Atropine
Atenolol	Cyclobenzaprine	Benztropine
Beclometasone dipropionate	Cyproheptadine	Chlorpheniramine
Bupropion hydrochloride	Loxapine	Chlorpromazine
Captopril	Meperidine	Clemastine
Chlorthalidone	Methotrimeprazine	Clomipramine
Cimetidine hydrochloride	Molindone	Clozapine
Clorazepate	Oxcarbazepine	Darifenacin
Codeine	Pethidine hydrochloride	Desipramine
Colchicine	Pimozide	Dicyclomine
Dextropropoxyphene		Diphenhydramine
Diazepam		Doxepin
Digoxin		Flavoxate
Dipyridamole		Hydroxyzine
Disopyramide phosphate		Hyoscyamine
Fentanyl		Imipramine
Fluvoxamine		Meclizine
Furosemide		Nortriptyline
Haloperidol		Orphenadrine
Hydralazine		Oxybutynin
Hydrocortisone		Paroxetine
Isosorbide preparations		Perphenazine
Loperamide		Procyclidine
Metoprolol		Promazine
Morphine		Promethazine
Nifedipine		Propantheline
Prednisone/Prednisolone		Pyrilamine
Quinidine		Scopolamine
Ranitidine		Thioridazine (withdrawn)
Theophylline		Tolterodine
Timolol maleate		Trifluoperazine
Trazodone		Trihexyphenidyl
Triamterene		Trimipramine
Warfarin		

Anticholinergic burden (ACB) scale

Boustani MA et al. Aging Health. 2008;4(3):311-20. Campbell N et al. Clinical Interventions in Aging. 2009;4(1):225-33

Score > 3 clinically relevant

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I am sorry to bother you, but as a patient on Detrusitol, 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

Excerpt from patient's letter 2.2015

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Cumulative Use of Strong Anticholinergics and Incident Dementia
A Prospective Cohort Study

Shelly L. Gray, PharmD, MS; Melissa L. Anderson, MS; Sascha Dublin, MD, PhD; Joseph T. Hanlon, PharmD, MS; Rebecca Hubbard, PhD; Rod Walker, MS; Onchee Yu, MS; Paul K. Crane, MD, MPH; Eric B. Larson, MD, MPH

JAMA Internal Medicine
2015

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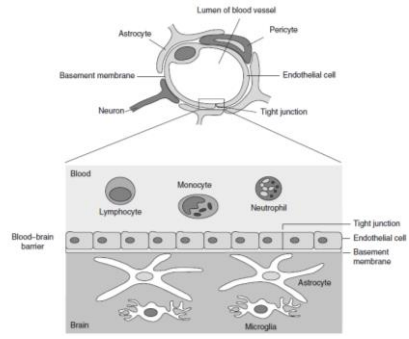

Chancellor et al. Drugs Aging 2012

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Transport across the blood brain barrier

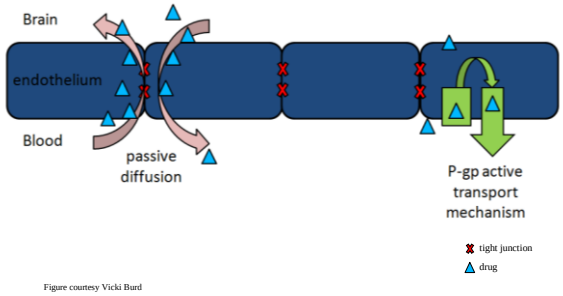

Figure courtesy Vicki Burd

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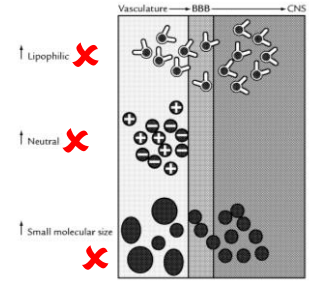
Aability to cross the blood brain barrier



Trospium chloride

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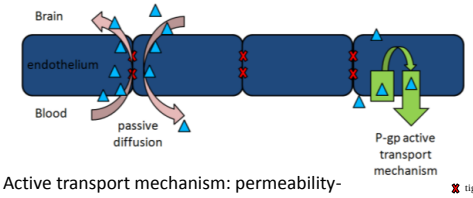
Active efflux across the blood brain barrier



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

Figure courtesy Vicki Burd

1.Ramakrishnan P. EQJBM. 2003; 19:160-165;
2. Wagg A et al. IJCP. 2010; 64(9): 1279-1286;
3. Chancellor et al. Drugs Aging. 2012; 29(4):259-273

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Selective Muscarinic receptor binding: M3 versus M1 receptor

Agent	Formulation	Dosing	Dose	Chemical Structure	Muscarinic M_2:M_3 Affinity (K_i Ratios)*
Darifenacin[4,5]	Controlled release	Once daily	7.5, 15 mg	Tertiary amine	9.3
Oxybutynin[5,6]	Immediate release	Two or three times daily	5 mg	Tertiary amine	1.5
	Extended release	Once daily	5, 10, 15, 20 mg		
	Skin patch	3–4 days	3.9 mg/d		
Solifenacin[7,8]	Controlled release	Once daily	5, 10 mg	Tertiary amine	2.5
Tolterodine[5,9]	Immediate release	Twice daily	1, 2 mg	Tertiary amine	0.6
	Extended release	Once daily	2, 4 mg		
Trospium[5,10]	Immediate release	Twice daily (at least 1 hour before food)	20 mg	Quaternary amine	1.5

Darifenacin

ICS 2015 Montreal

Notes