Neurogenic Bladder and Sexual Dysfunction

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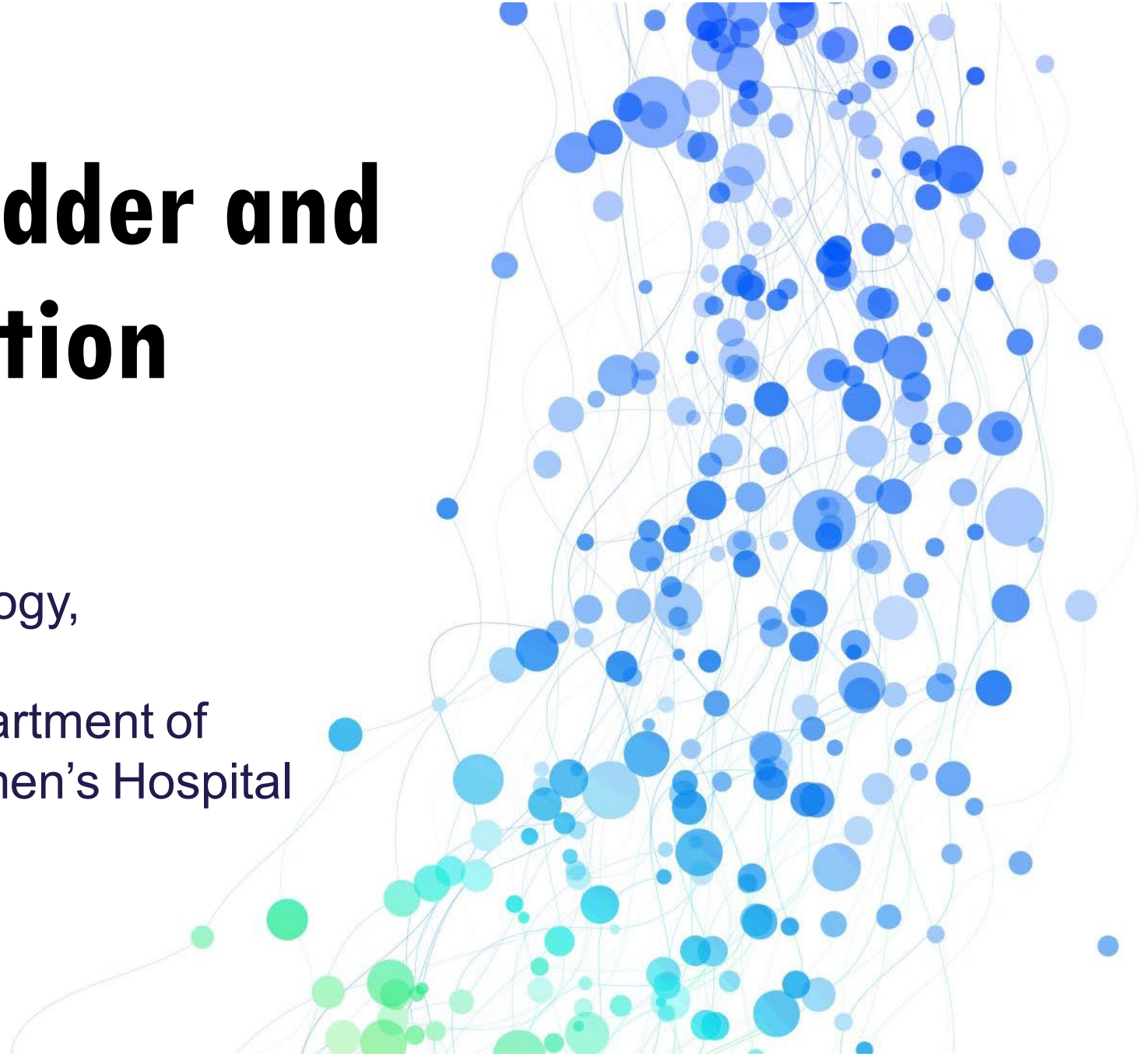
Brigham MS Center



Disclosures

Tamara Kaplan MD

- Served on scientific advisory boards for Novartis, EMD Serono and Genentech

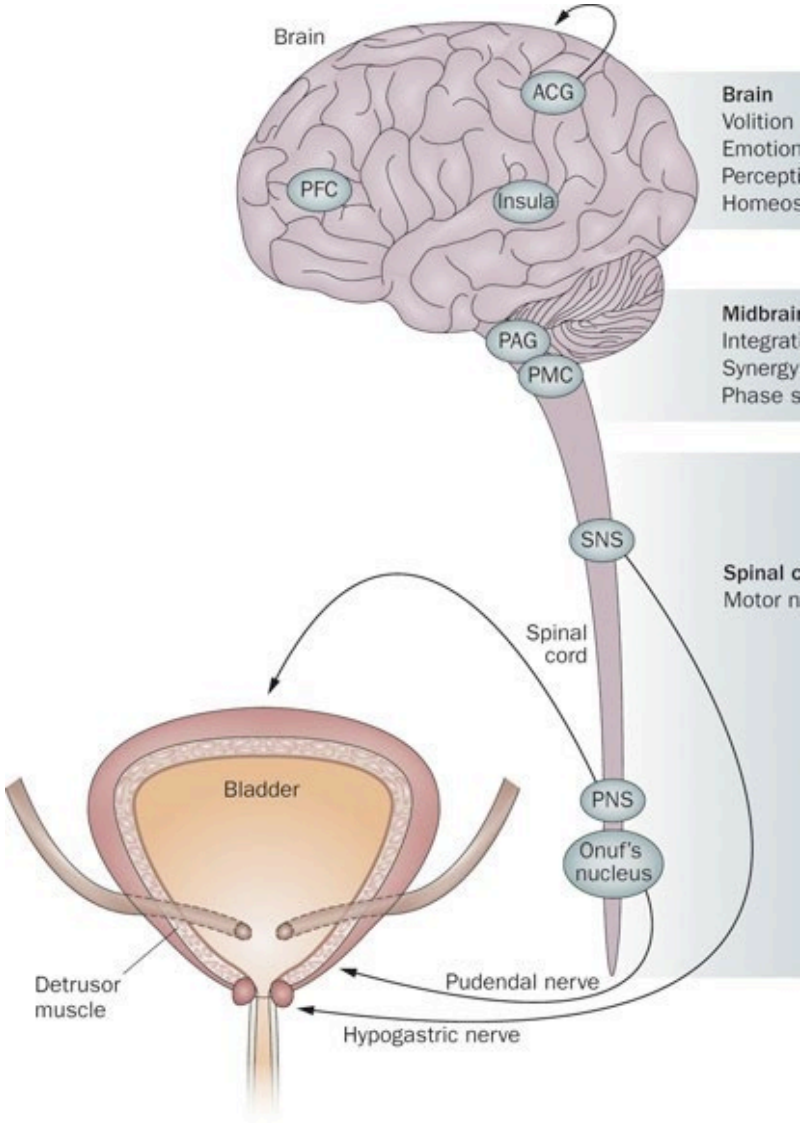
Outline

Normal Bladder Function

- Neural control of the lower urinary tract
  - Storage
  - Voiding

Disordered Bladder Function

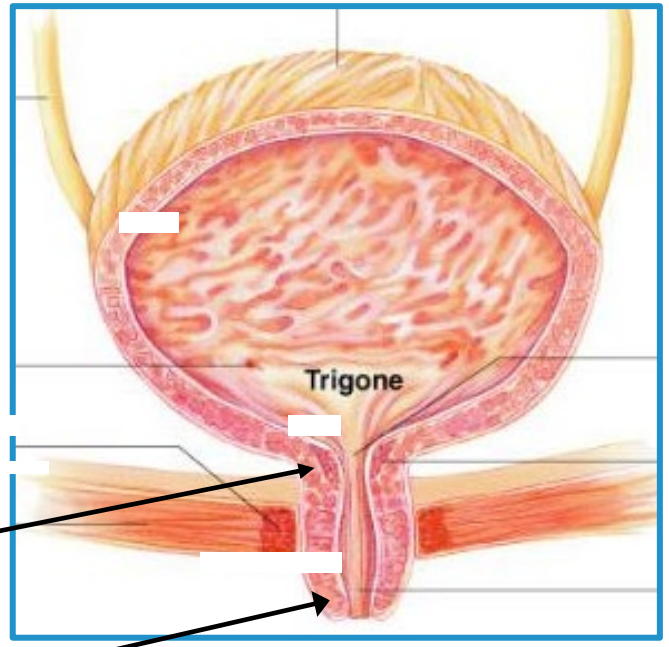
- Lower Urinary Tract Symptoms
- Localization Principles
- Three Patient Cases: Managing Neurogenic Bladder Dysfunction



Anatomy of the Lower Urinary Tract

3 Components:

1. **Bladder**: (detrusor) *smooth muscle*
   Capacity 400-600cc, typically higher capacity in men
2. **Internal Urethral Sphincter (IUS)** *smooth muscle,* natural tone keeps bladder neck empty of urine
3. **External Urethral Sphincter (EUS)** – voluntary *skeletall/striated muscle*
   - More extensive and thick in men

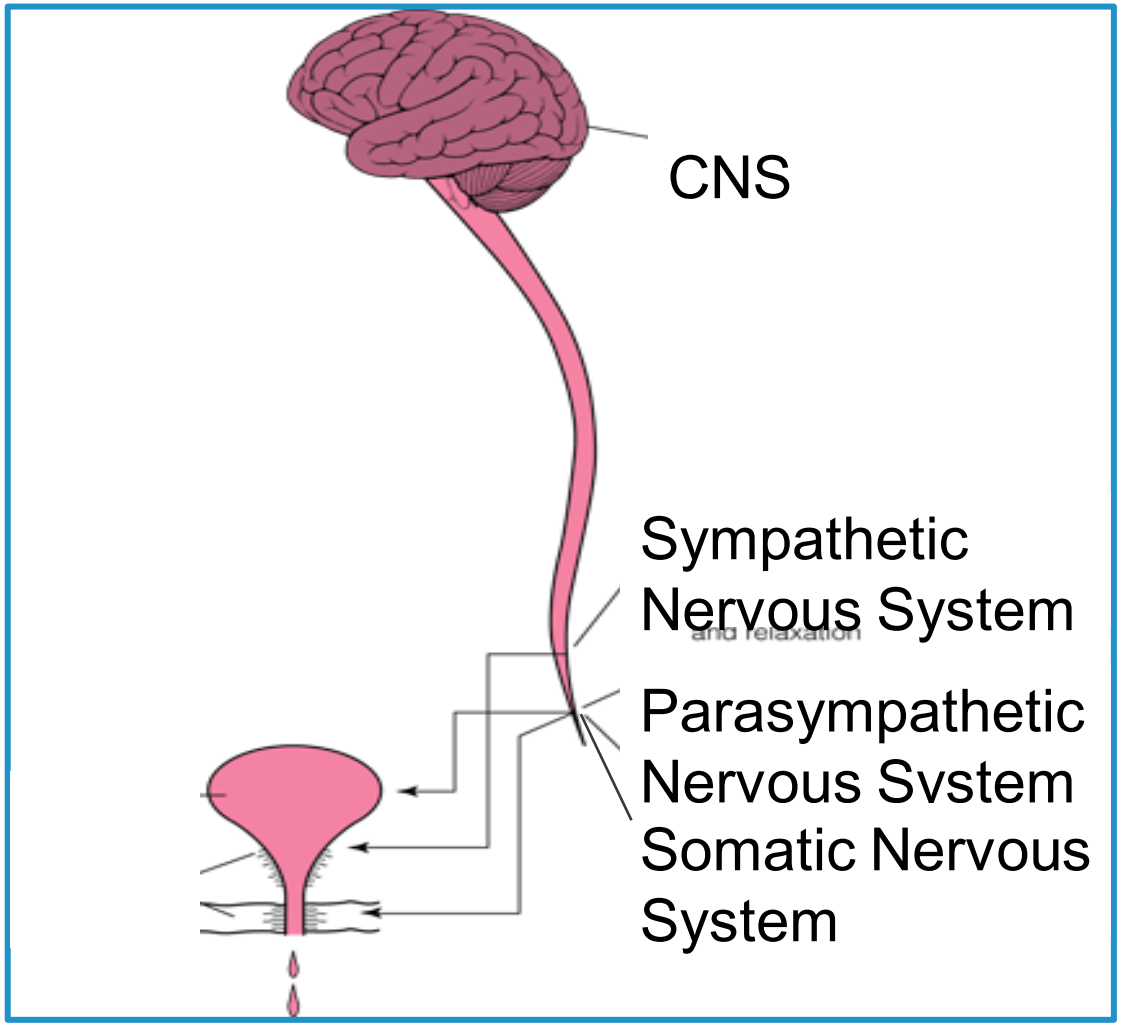


2 Roles:

1. Storage ofå Urine
2. Void at appropriate times

The Symphony: Conducting Bladder Control

- CNS: Brain signals to initiate and control urination
- Autonomic Nervous System
  - Sympathetic: Storage
  - Parasympathetic: Voiding
- Peripheral Nerves: Relay messages between CNS and LUT



Phases of Bladder Function

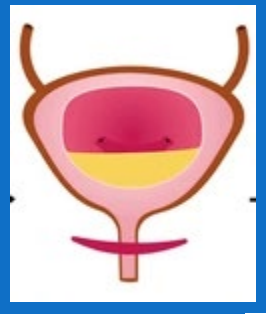
Function	Efferent Innervation	Action
Storage	Sympathetic T11-L2 (NE)	Detrusor muscle **relaxation**, Internal sphincter **contraction**
Voiding		
Voluntary control		

Controlling the Lower Urinary Tract: Storage

Storage Phase – 98% of time:

Sympathetic

- Internal Urethral Sphincter contracted
- Detrusor relaxed
- Sympathetic activation & Parasympathetic deactivation



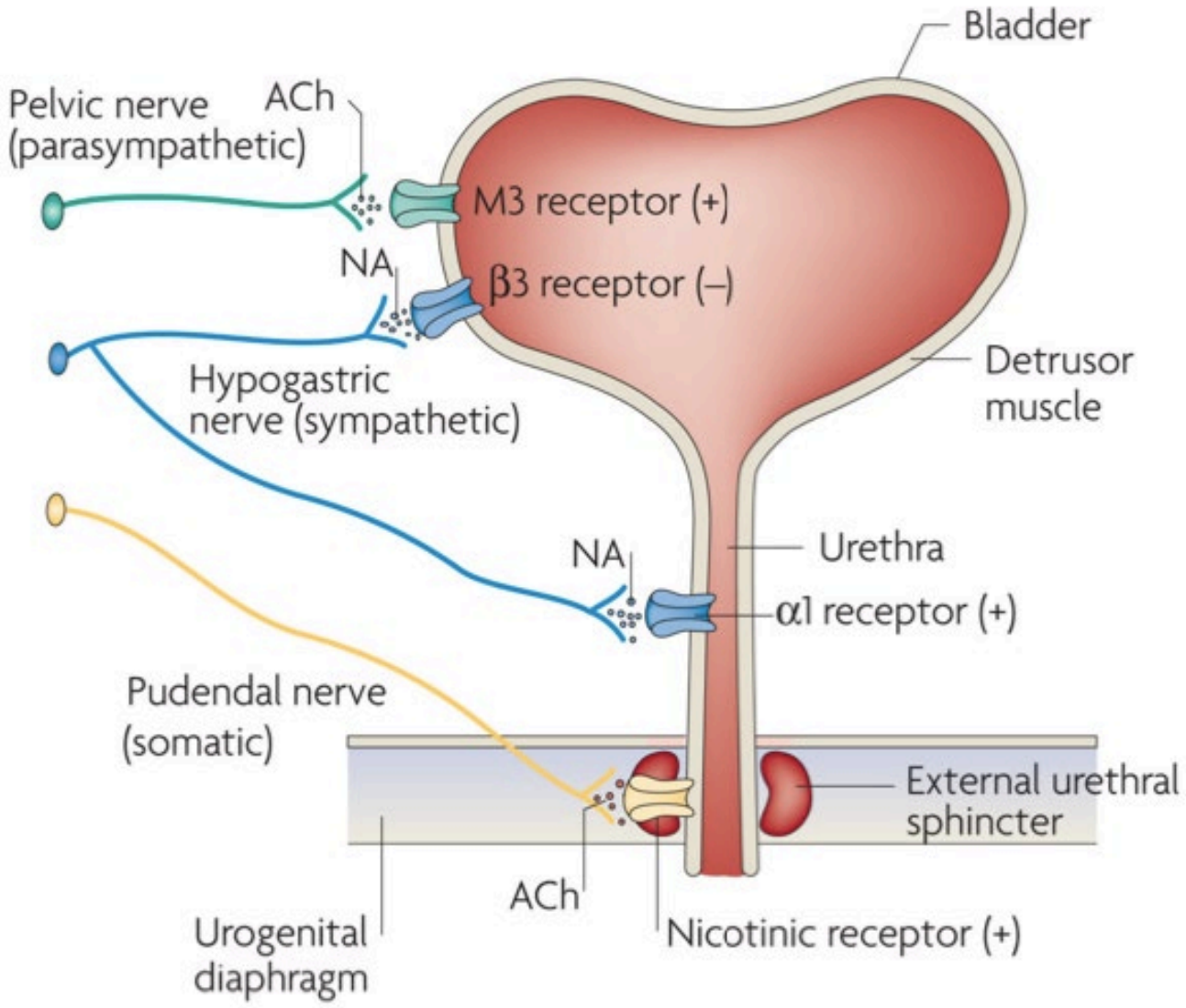
Storage Phase

Sympathetic Activation:

- Detrusor Muscle: Relaxed
  - β3 adrenergic receptors
- Internal Urethral Sphincter: Closed
  - α1 adrenergic receptors

Somatic Nervous System:

- External Sphincter: Closed
  - Nicotinic cholinergic receptors



Controlling the Lower Urinary Tract: Storage

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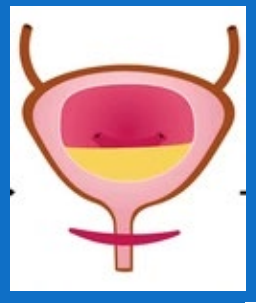
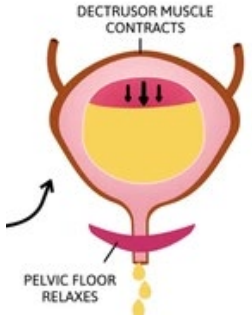


Controlling the Lower Urinary Tract: Voiding

Voiding Phase

Parasympathetic

- Internal Urethral Sphincter relaxed
- Detrusor contracted
- Sympathetic activation & Parasympathetic deactivation

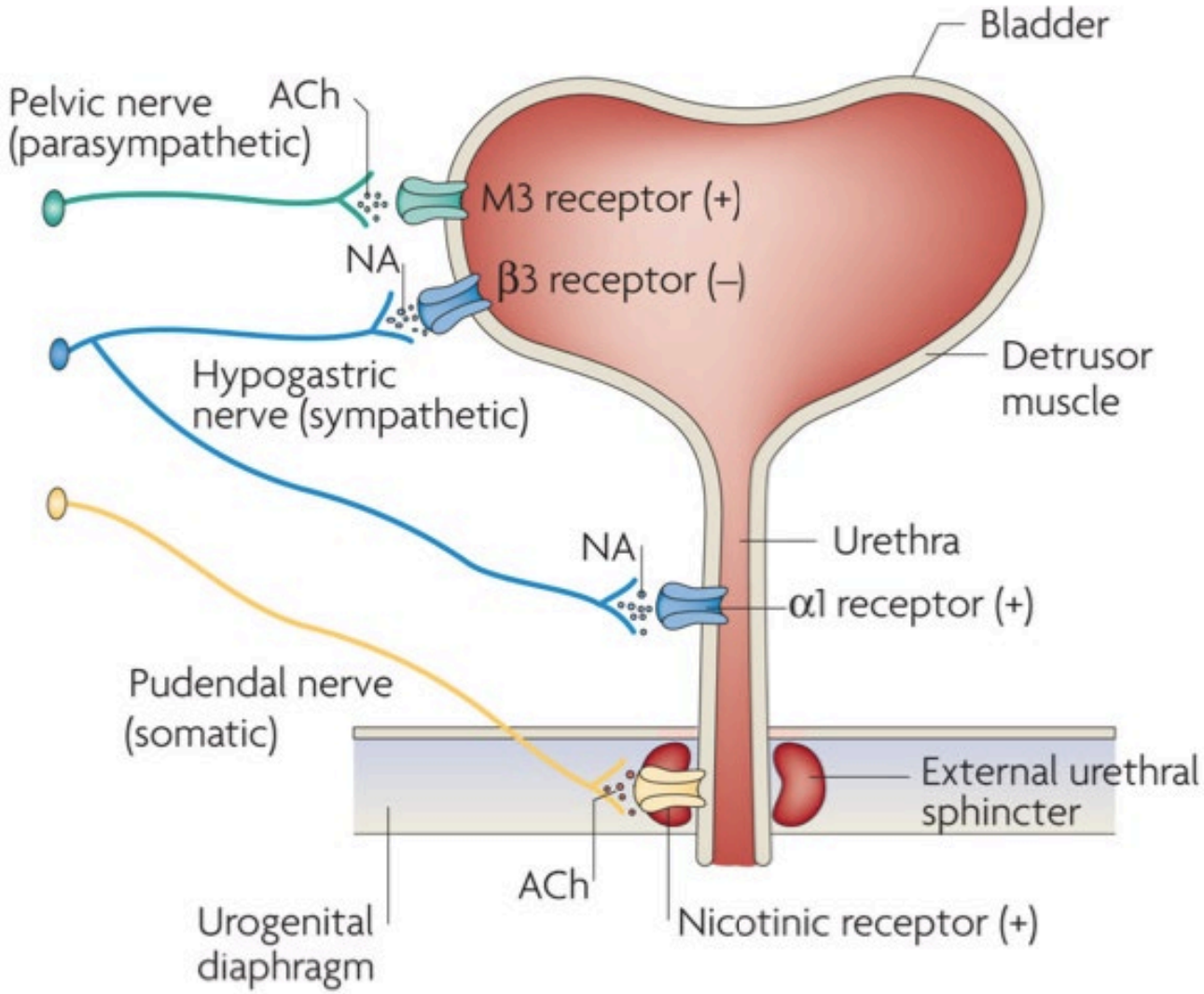


Voiding Phase

Parasympathetic Activation:
- Detrusor Muscle: Contraction
  - M3 muscarinic receptors

Inhibition of sympathetic outflow
- Internal sphincter: Relaxed

Inhibition of somatic nervous system
- External sphincter: Relaxed



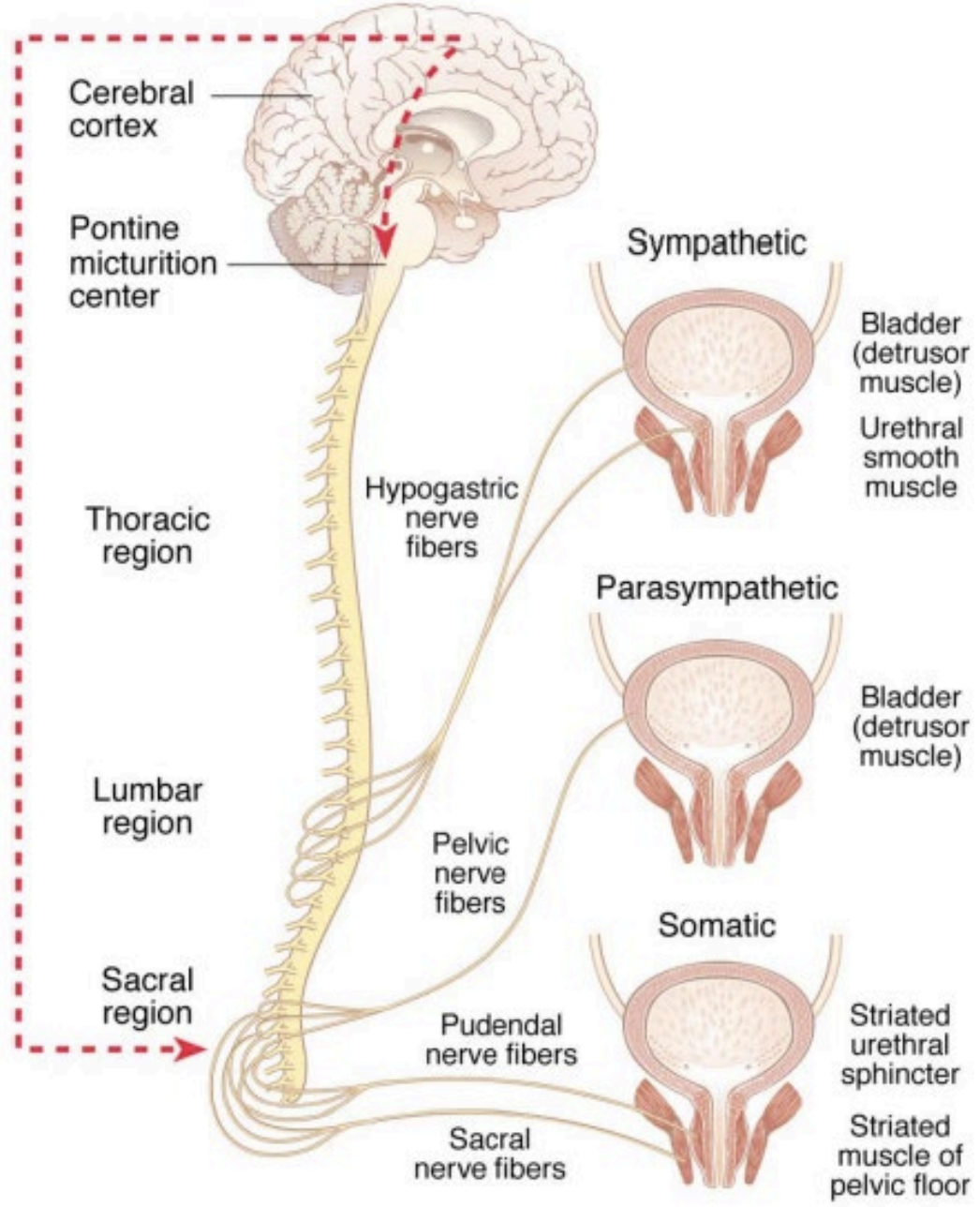
Phases of Bladder Function

Function	Efferent Innervation	Action
Storage	Sympathetic T11-L2 (NE)	Detrusor muscle **relaxation**, Internal sphincter **contraction**
Voiding	Parasympathetic S2,3,4 (Ach)	Detrusor muscle **contraction**, Internal sphincter **relaxation**
Voluntary control	Somatic (pudendal nerve) (Ach)	Initiate or inhibit micturition through cortical control External sphincter **contraction**

Brain in the Bathroom: Unique Control of Bladder Function

Unique Collaboration: **Autonomic** AND Voluntary control

- **Initiated by Choice**
- **Social Cues**
- **Learned Behavior**
- **Fullness Feedback**



Micturition Reflex - Coordinating Storage & Micturition - Brain in Control

Frontal Lobes & Basal Ganglia:
Inhibit urination signals—conscious decisions.

Periaqueductal Gray (PAG):
Relay center for bladder sensations.

Insula, Hypothalamus:
Process bladder signals.

Pontine Micturition Center (PMC):

- Coordinates urinary sphincters and bladder
- Switch – from 'storage' to 'voiding' phase

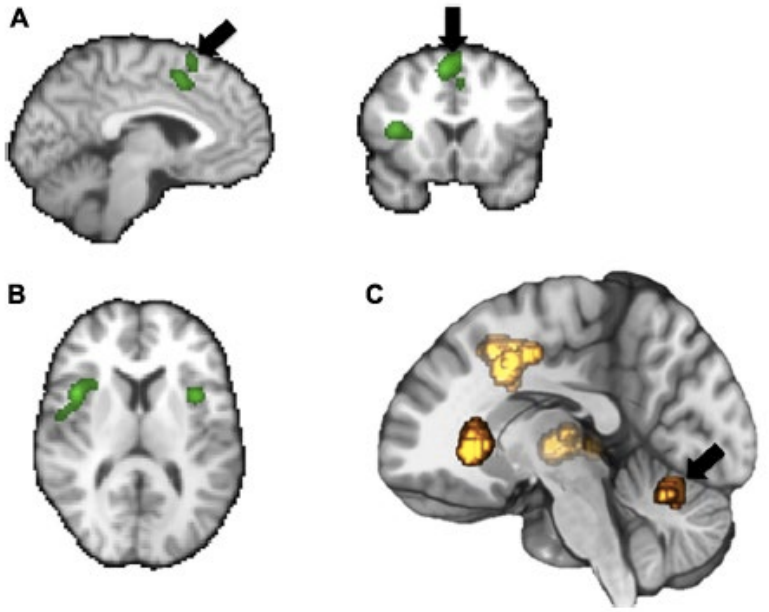
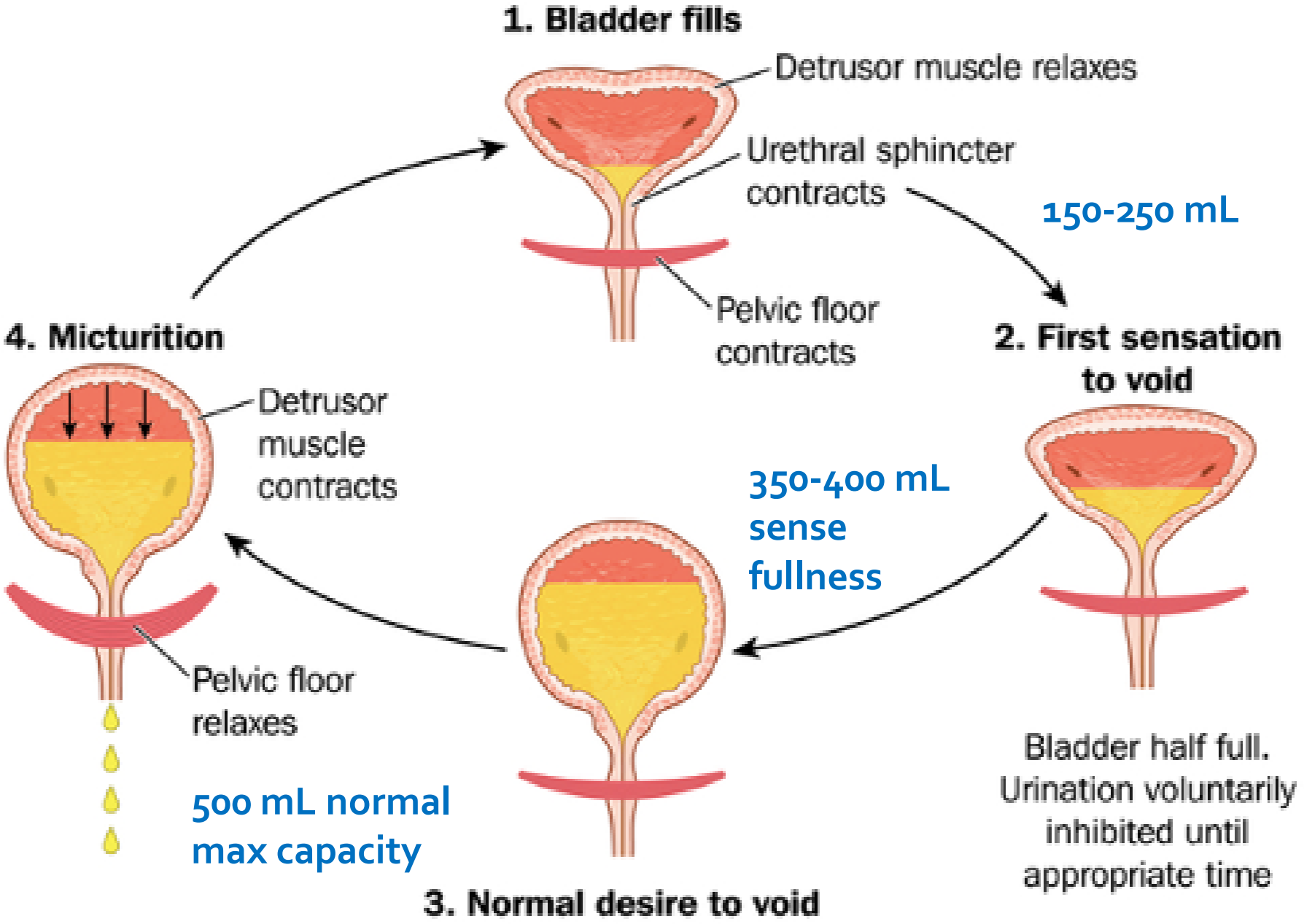


FIGURE 3 | Summary of some key brain areas demonstrated to be involved in bladder related tasks based on fMRI: supplementary motor area (SMA), mid-cingulate gyrus **(A)**, frontal operculum **(B)**, insula **(C)**, cerebellum.

Normal Micturition Cycle



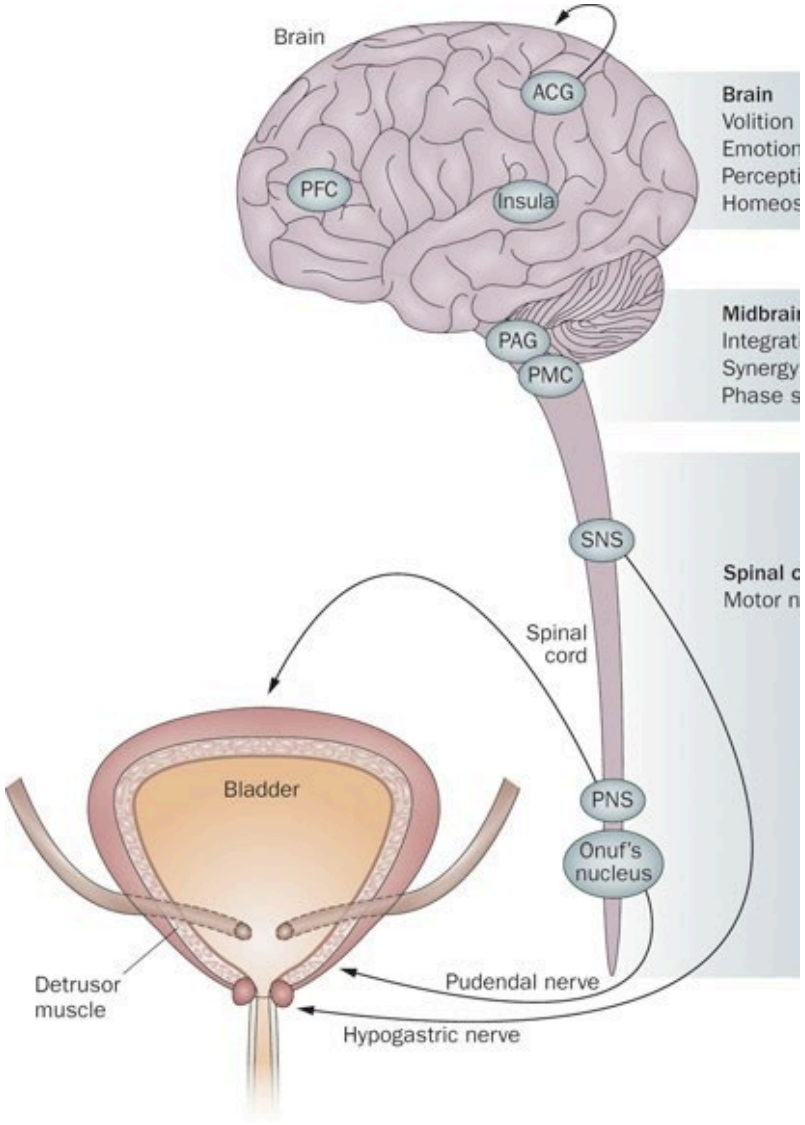
Outline

Normal Bladder Function

- **Neural control of the lower urinary tract:**
  - **Storage**
  - **Voiding**

Disordered Bladder Function

- **Lower Urinary Tract Symptoms (LUTS)**
- **Localization Principles**
- Three Patient Cases: Managing Neurogenic Bladder Dysfunction



Disruptions in Normal Bladder Function: Lower Urinary Tract Symptoms (LUTS)

Storage

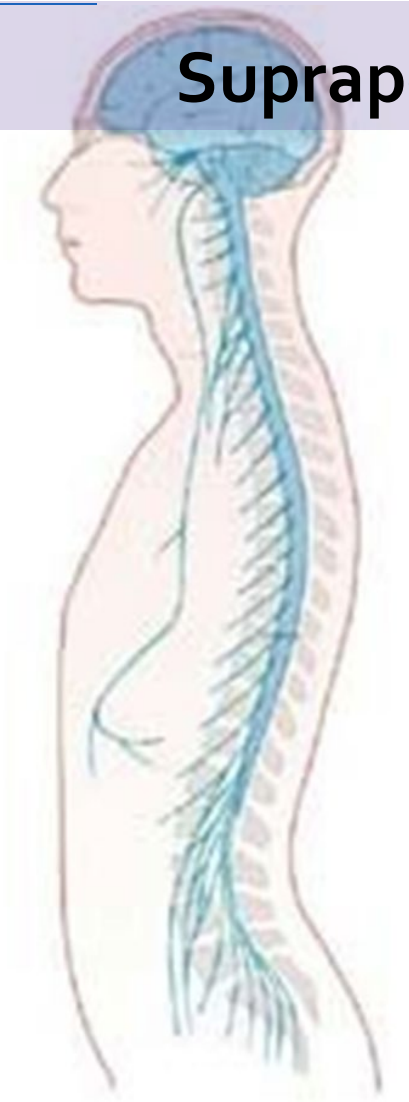
- Urgency
- Incontinence
- Nocturia***
- Frequency***

Voiding

- Hesitancy/straining
- Retention
- Interrupted/poor urinary stream
- Sensation of incomplete emptying
- Terminal dribble
- Double voiding
- Nocturia***
- Frequency***

Supra pontine lesion

Suprapontine

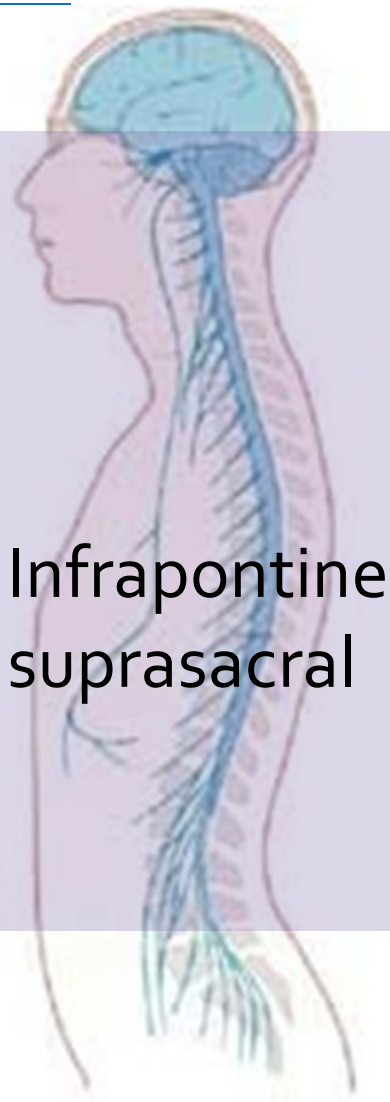


Diagnoses:
Stroke, Brain Injury, Cerebral Palsy; Degenerative: Parkinson Disease, MSA, Alzheimer's

Symptoms:
Storage symptoms, urinary urgency and incontinence, detrusor overactivity

Panicker et al. Lancet Neurol. 2015; de Groat. commonfund.nih.gov

Infrapontine-suprasacral lesion

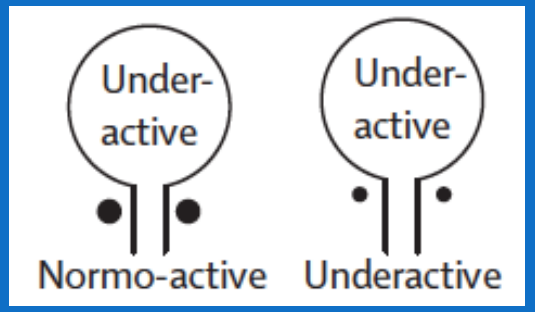


Infrapontine-suprasacral

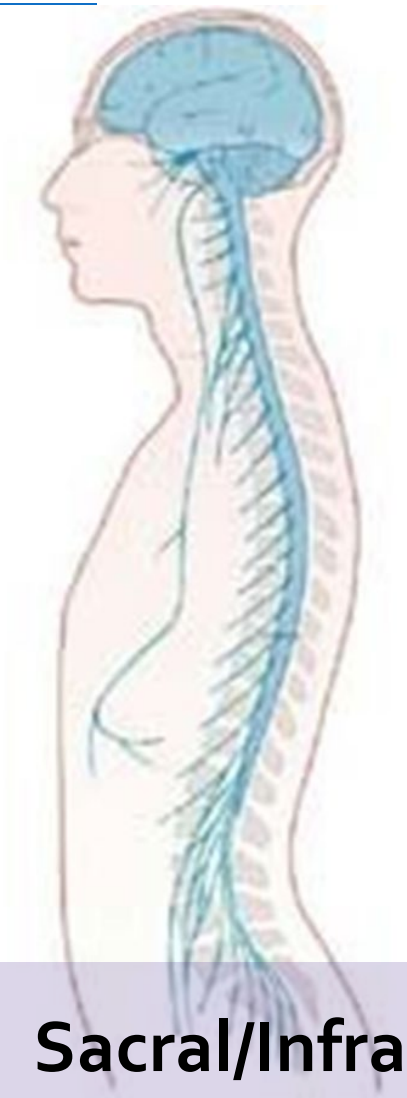
Diagnoses:
Myelopathy, SCI, Multiple sclerosis

Symptoms:
Storage and voiding symptoms: urinary urgency, incontinence, hesitation, retention
Detrusor–sphincter dyssynergia

Panicker et al. Lancet Neurol. 2015; de Groat. commonfund.nih.gov



Sacral/ Infrasacral lesion



Diagnoses:
conus medullaris and cauda equina syndrome

Symptoms:
Voiding symptoms: hesitancy, retention
Detrusor underactivity

Sacral/Infrasacral

Panicker et al. Lancet Neurol. 2015; de Groat. commonfund.nih.gov

Assessment Tools and Diagnostics

- Interpret symptoms based on knowledge of the neurological control of bladder functions
- **Assessment Tools**
  - History & Physical Exam: Focus on bladder and neurological functions.
  - Bladder Diaries: Track micturition times, volumes, and incontinence.
  - Urinalysis: Rule out infections and other non-neurological causes.
- **Advanced Diagnostics**
  - Measure PVR
  - Urodynamics: Evaluate bladder and urethra functionality.

Case 1

Patient with Multiple Sclerosis

Case 1 – Multiple Sclerosis

- 36 F diagnosed with MS 10 years ago.
- Paresthesias in both legs up to T4 level. Notes urinary frequency
- Exam: Left RAPD +, Strength. LUE and Lower extremities bilaterally 4/5, Decreased vibration sense in both legs

Case 1 – Multiple Sclerosis

Storage	Voiding
Bladder sensations: A constant sensation of need to urinate.	Initiating voiding: difficulty starting a stream, keeping it going
Urgency: sometimes	Hesitancy: Yes, occasional abdominal straining
Daytime frequency: 10 x	Quality of stream: interrupted
Nocturia: 2 x during the night	Dysuria: No
Urinary incontinence: Yes, sometimes with associated urge to void	Abdominal straining when voiding: No
Voided Volumes: up to 50ml	Sensation of incomplete bladder emptying after the void: yes
	Double voiding: no

Patient case study 1 – LUTS Workup

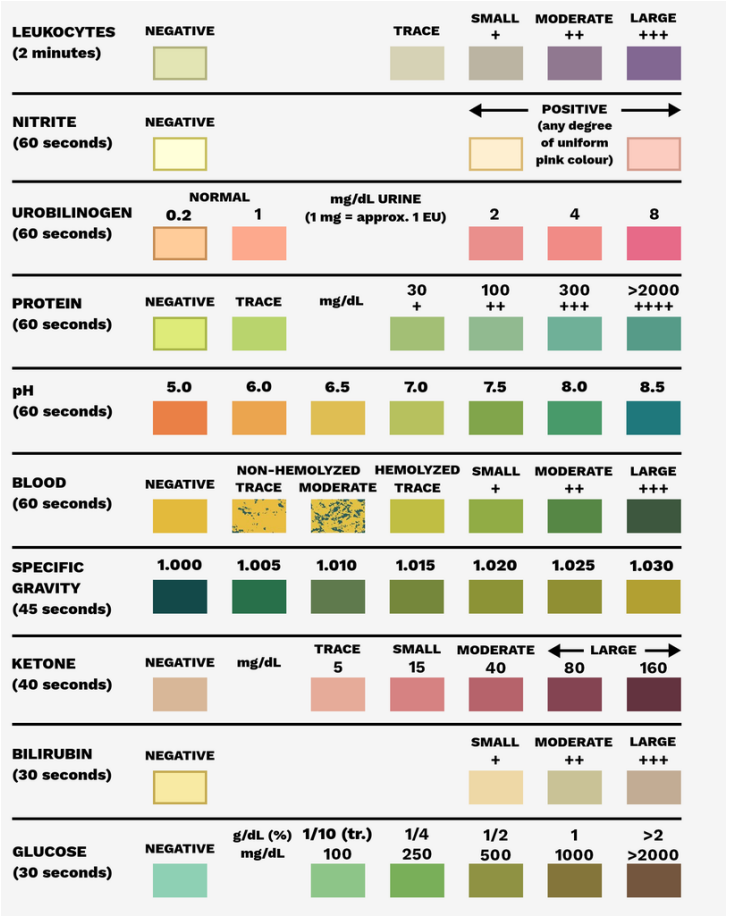
STEP 1

Urinalysis (dipstick testing)

- Should be performed at initial evaluation
- Should be performed when clinically indicated at follow-up visits

Table 2 Algorithm performance

	Table 1 A (%)	Table 1 B (%)	Table 1 C (%)
Specificity	78	80	99
Sensitivity	75	75	54
Positive predictive value	30	32	83
Negative predictive value	96	96	94



Rakusa M, Eur J Neurol, 2012

Patient case study 1

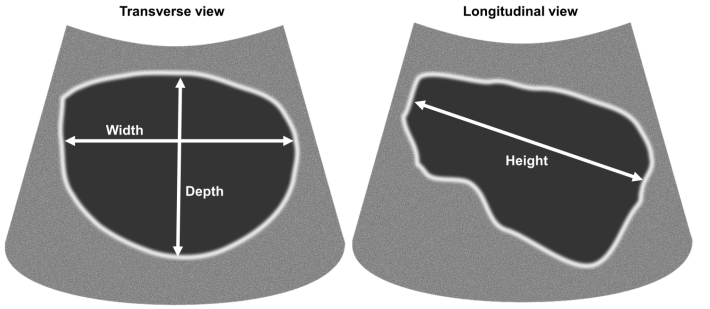
Step 2

Bladder Diary

DAY 3					
Time	Fluids In	Urination		Leakage	
	How much did you drink (ml)?	Urine passed (ml)	Sudden strong urge to pee?	Did you leak? (Please tick)	Why did you leak? (See page 1)
11.00am	*150ml*	*100ml*	Yes / No	✓	*B*
			Yes / No		
			Yes / No		
			Yes / No		
			Yes / No		

Step 3

Measure PVR



PVR = 250 mL

Medina-Polo J, Neurourol Urodyn. 2020

Patient Update

- PVR: 250ml
- UA: Negative
- Bladder diary: frequent voids, with small volume, intermittent urgency and hesitancy
- Patient tried oxybutynin but developed several UTIs on the medication

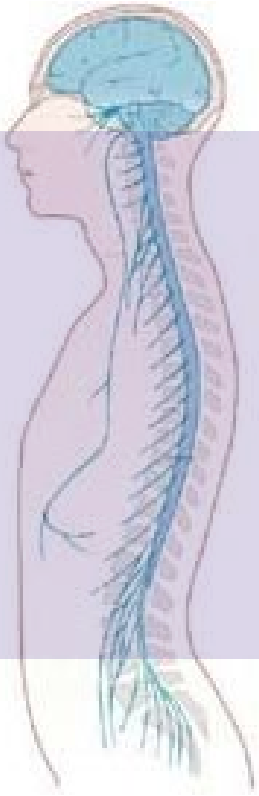
Voiding (↑↑↑ PVR) AND **Storage** symptoms (urgency, nocturia)

Antimuscarinics -- risk of retaining larger volumes of urine

Signs & Symptoms

- Both **storage** and **voiding** symptoms
- PVR urine volumes increased
- Detrusor is overactive; possible detrusor sphincter dyssynergia (DSD)
- Urethral tone is overactive
- Compliance decreased

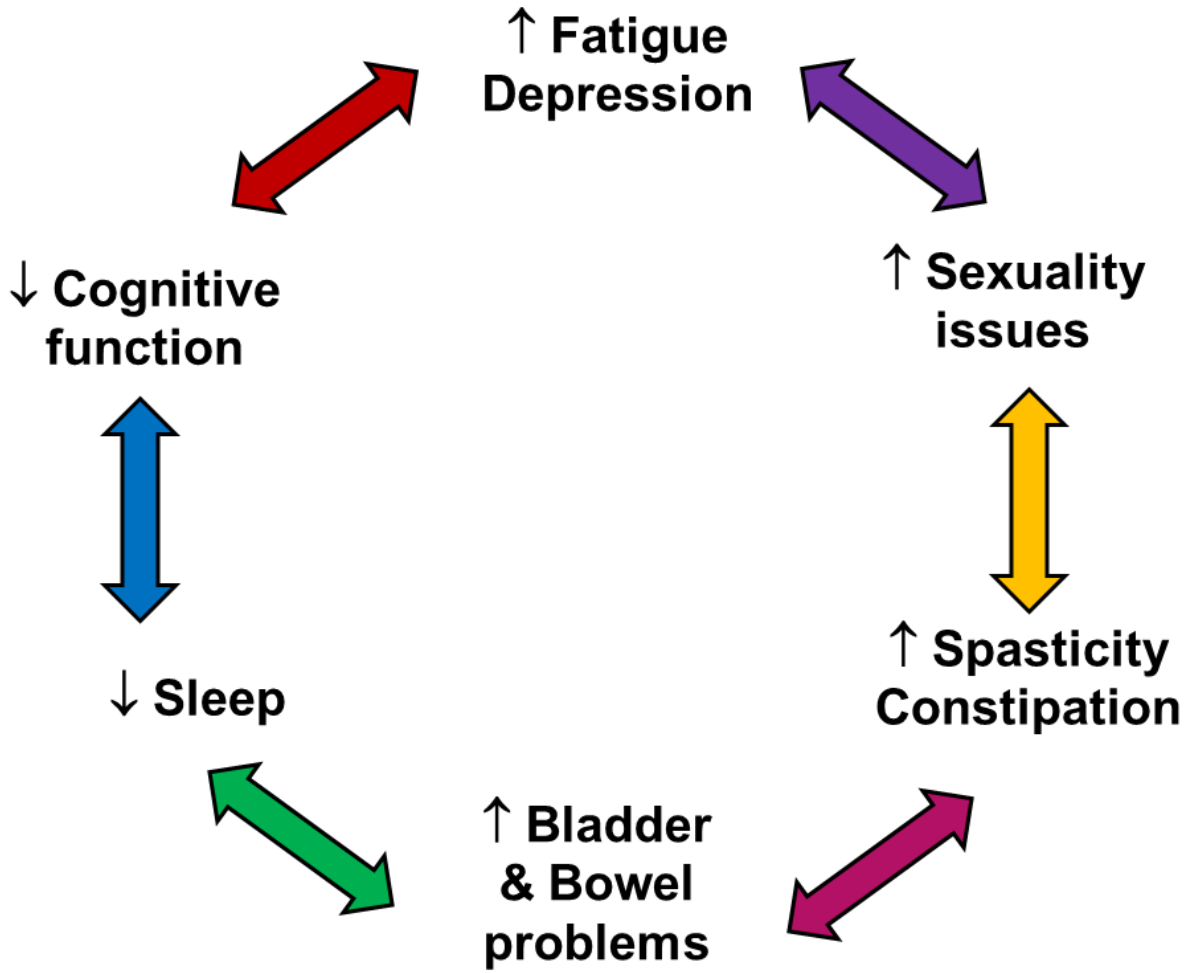
Infrapontine-Suprasacral



Treatment and Management

Infrapontine-Suprasacral

Patient Case Study 1 – Treatment and Management



Cycle of MS Symptoms

LUTS Prevalence & Management

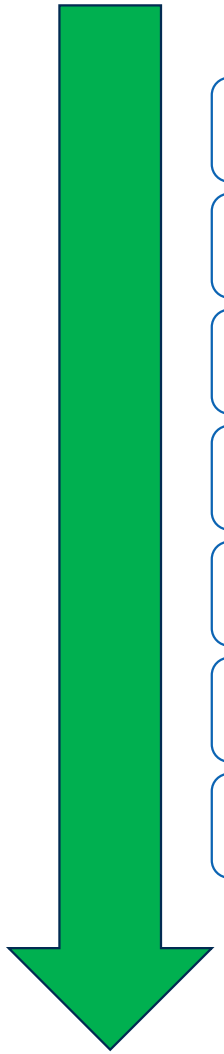
92% reported LUTS - regardless of gender (N=1047 patients with MS)

30% of those never sought treatment from HCPs

Reasons for not seeking treatment
Felt symptoms were not severe enough to discuss
Uncomfortable discussing symptoms with HCP
HCP did not ask
Believed HCP would not be able to help

Khalaf, K., et al. 2015

Treatment of Neurogenic Bladder



- Bladder training, Lifestyle modifications
- Pelvic Floor Rehab
- Pharmacologic: Antimuscarinics, $\beta 3$ agonists, α-antagonists
- Self Catheterization
- Electrical Stimulation
- Botulinum toxin
- Surgical Interventions

Treatment: Lifestyle Modifications

Smoking Cessation

Pelvic Floor PT/Kegals

Strengthen supporting muscles

Dietary Changes

Alcohol, caffeine, carbonated beverages

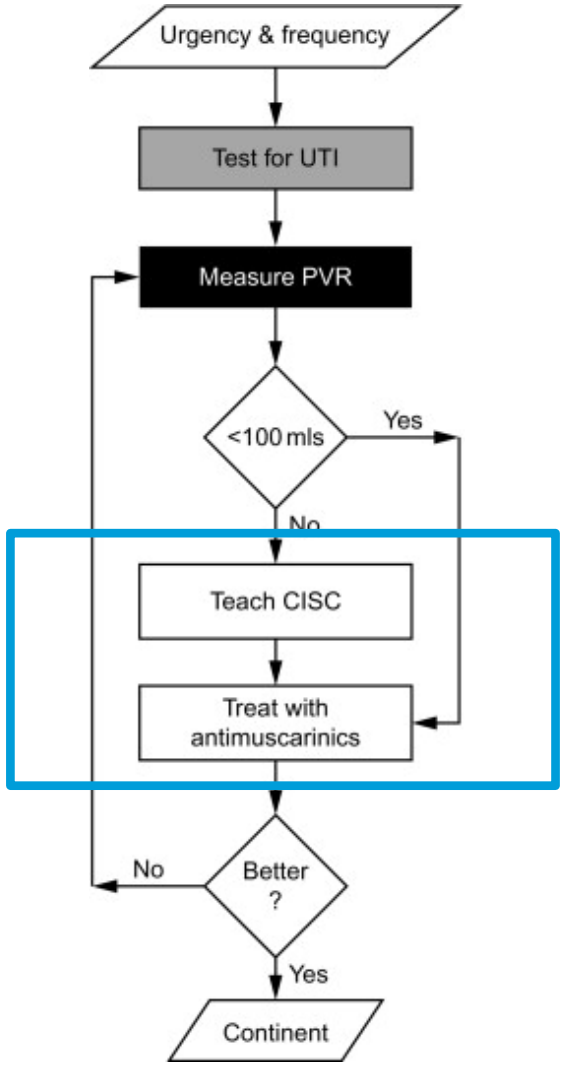
Avoid dehydration, but time fluid intake

Bladder Training
"Timed voiding"

For urgency and retention

Wear the right pads

Management Algorithm



Fowler, C. Panicker, J. N., 2015

Clean Intermittent Self Catheterization (CIC)

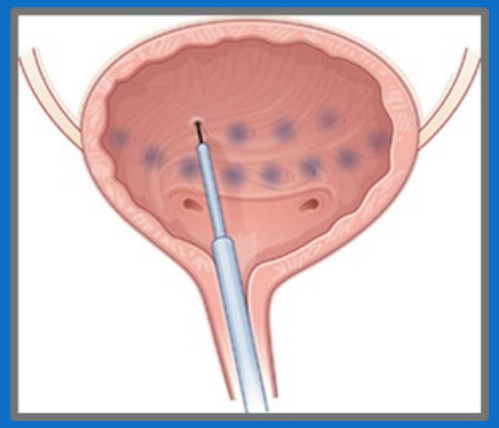
- CIC: Gold standard for treating voiding dysfunction.
- **Benefits:**
  - CIC significantly improves QoL and LUTS, such as:
    - Decreased urinary frequency.
    - Reduced urgency.
    - Lessened stress incontinence.
    - Diminished urgency incontinence.

Lapides J, et al., J Urol. 1972

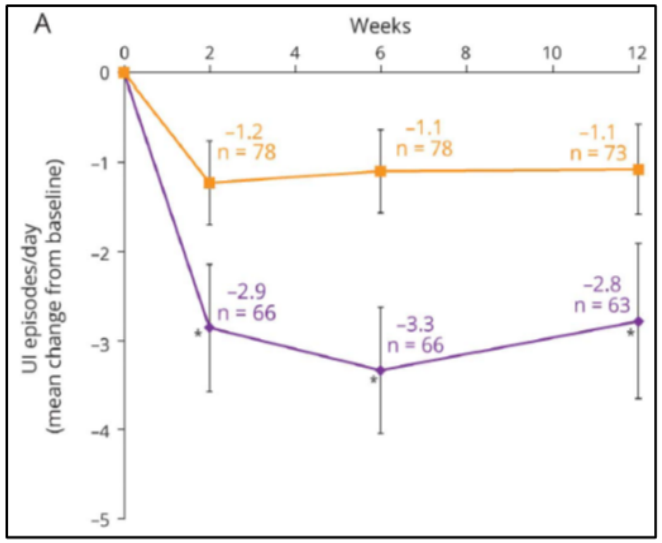
Castel-Lacanal E, et al. World J Urol. 2013

Luoto E, et al. Sairaanhoitaja 1993

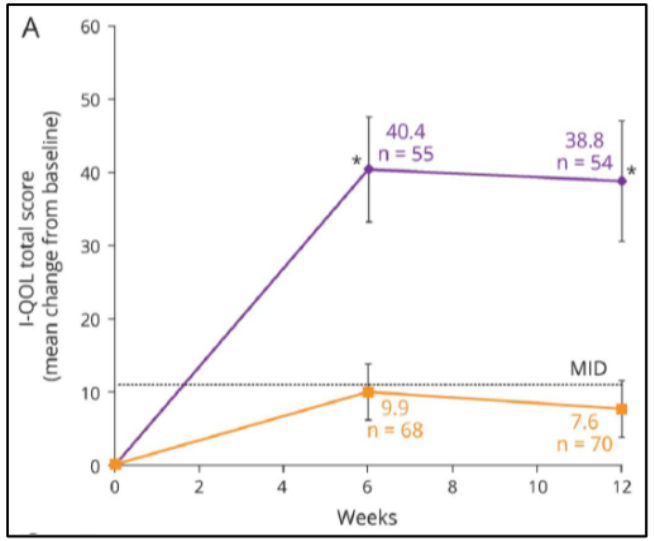
Intradetrusor Botulinum Toxin A for Neurogenic Bladder



- **Efficacy (Phase III Studies):**
  In MS & SCI patients, 200-300 units BoNT/A:



Improvement in incontinence episodes



Improvement quality of life

May cause urinary retention, necessitating CIC

Tullman M et al. *Neurology* 2018
Cruz F, et al. Eur Urol., 2011
Ginsberg D, et al. J Urol., 2012

Neuromodulation: Posterior Tibial Nerve Stimulation:

- 30-minute weekly sessions, 12 weeks.
- **Efficacy:** Meta-analysis shows PTNS and TTNS are effective and safe for neurogenic LUT dysfunction treatment.
- **MS patients:** Multicenter, prospective trial, TTNS (n=70)
  - **Result:** 82.6% (D30), 83.3% (D90) in urgency/frequency. Improved continence, QOL, symptom scores
- **Guideline supported:** American & Canadian Urologic Associations

Percutaneous (PTNS) & Transcutaneous (TTNS)

Schneider MP et al., 2015
Ginsberg D, et al. The AUA/SUFU guideline. *The Journal of urology* 2021
Kavanagh, A., et al., Canadian Urological Association guideline. Can Urol Assoc J, 2019
De Seze, et al. Neurourology and urodynamics. 2011

Case Summary: Treatment & Management

- Patient initiated Clean Intermittent Catheterization (CIC)
- Received Intradetrusor Botulinum toxin injections
- Current CIC schedule: every 4 hours during daytime and once before bedtime
- Improvement noted in urinary frequency and urgency
- No further UTIs reported since treatment

Case 2

Patient with Parkinson’s Disease

Case 2 – Parkinson's Disease

- 72 woman, Intermittent fainting episodes,
- Walking difficulties
- LUTS
- Exam: Hypomimia, Bradykinesia, Rigidity of all extremities, resting tremor, left hand

Case 2 – Parkinson's Disease

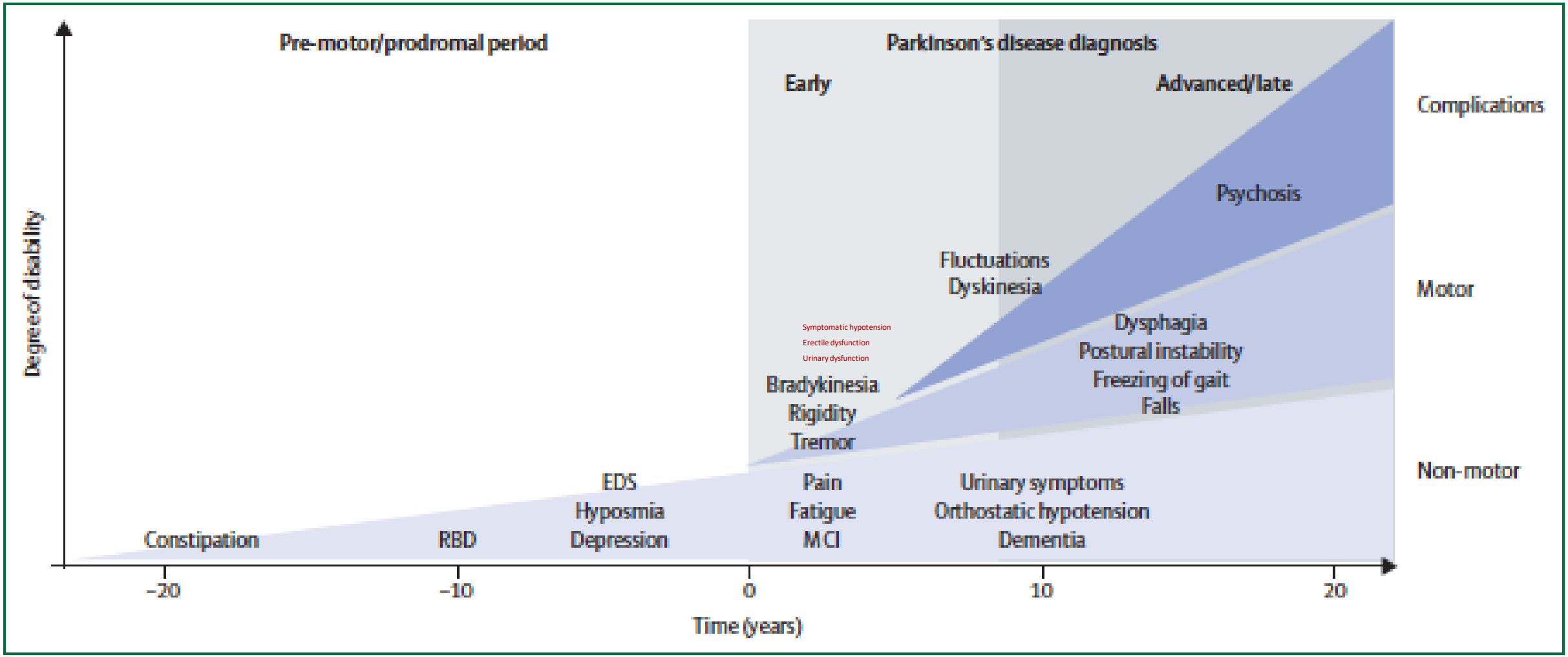
Storage	Voiding
Bladder sensations: A constant sensation of need to urinate.	Posture adopted during voiding: No
Urgency: Yes	Hesitancy: No
Daytime frequency: 8-10 x during the day	Quality of stream: normal voiding
Nocturia: 2 x during the night	Dysuria: No
Urinary incontinence: No	Abdominal straining when voiding: No
	Sensation of incomplete bladder emptying after the void: No
	Double voiding: No

Patient case study 2: Treatment and Management

Bladder Diary revealed:

- Increase urinary frequency - ~10x/day, 3x/night
- Frequent episodes of sudden, strong urge to urinate
- Difficulty controlling urgency, some episodes of urgency incontinence

Lifestyle modifications including limiting caffeine, carbonated beverages and timed voiding were discussed .



Dysautonomia in PD

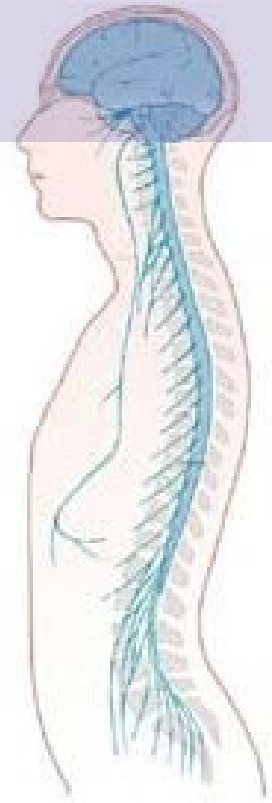
Kalia, Lancet, 2015

Signs & Symptoms

Primarily **storage** signs and symptoms:

- Low PVR, ~50ml
- Urgency
- Frequency
- Urgency incontinence
- Nocturia
- Heightened bladder-filling sensation

Suprapontine



Treatment and Management

Supratentorial Lesions

Pharmacologic Targets

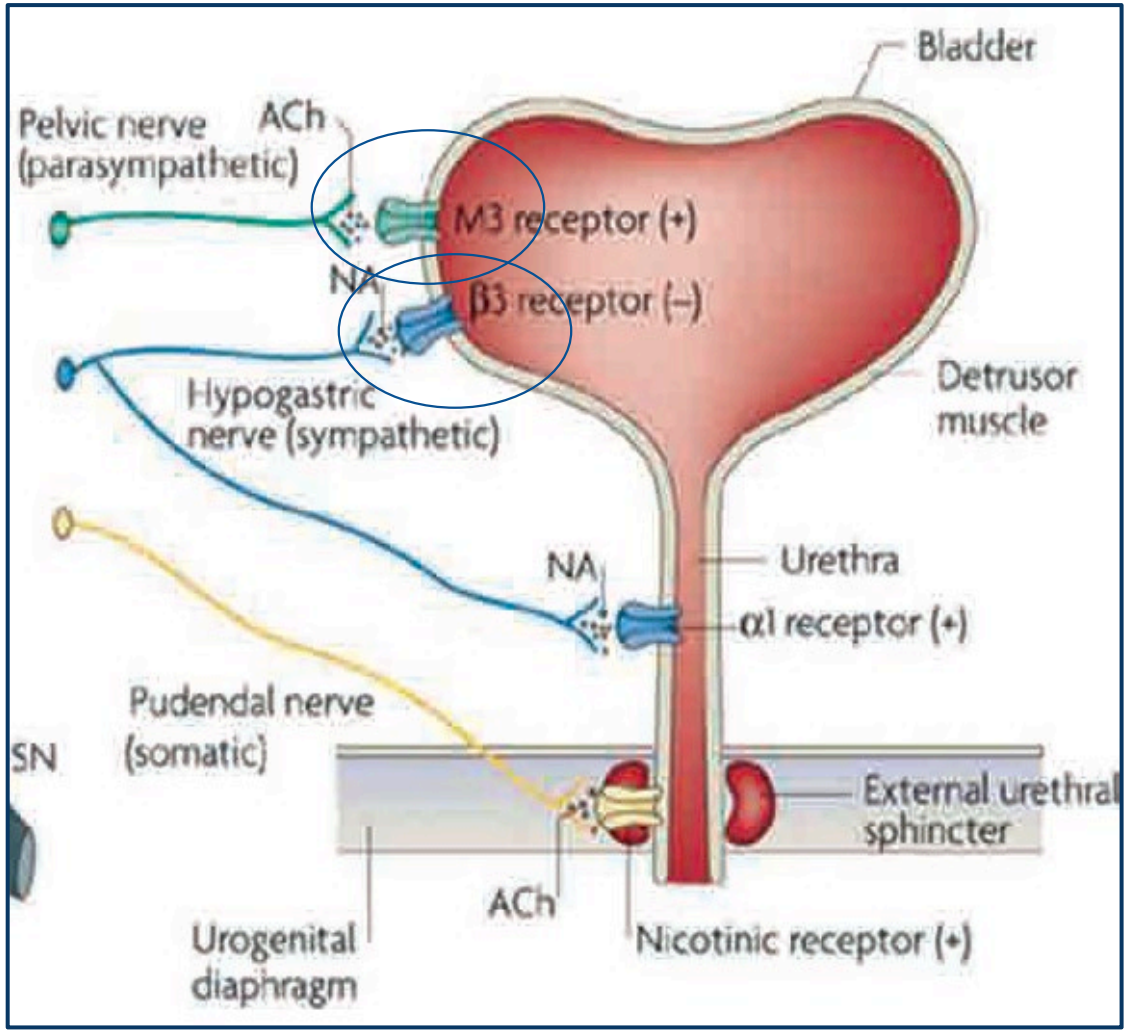
Storage:
Detrusor inhibition
Sympathetic – **β3**

Voiding
Detrusor contraction
Parasympathetic – **M3**

Parasympathetic

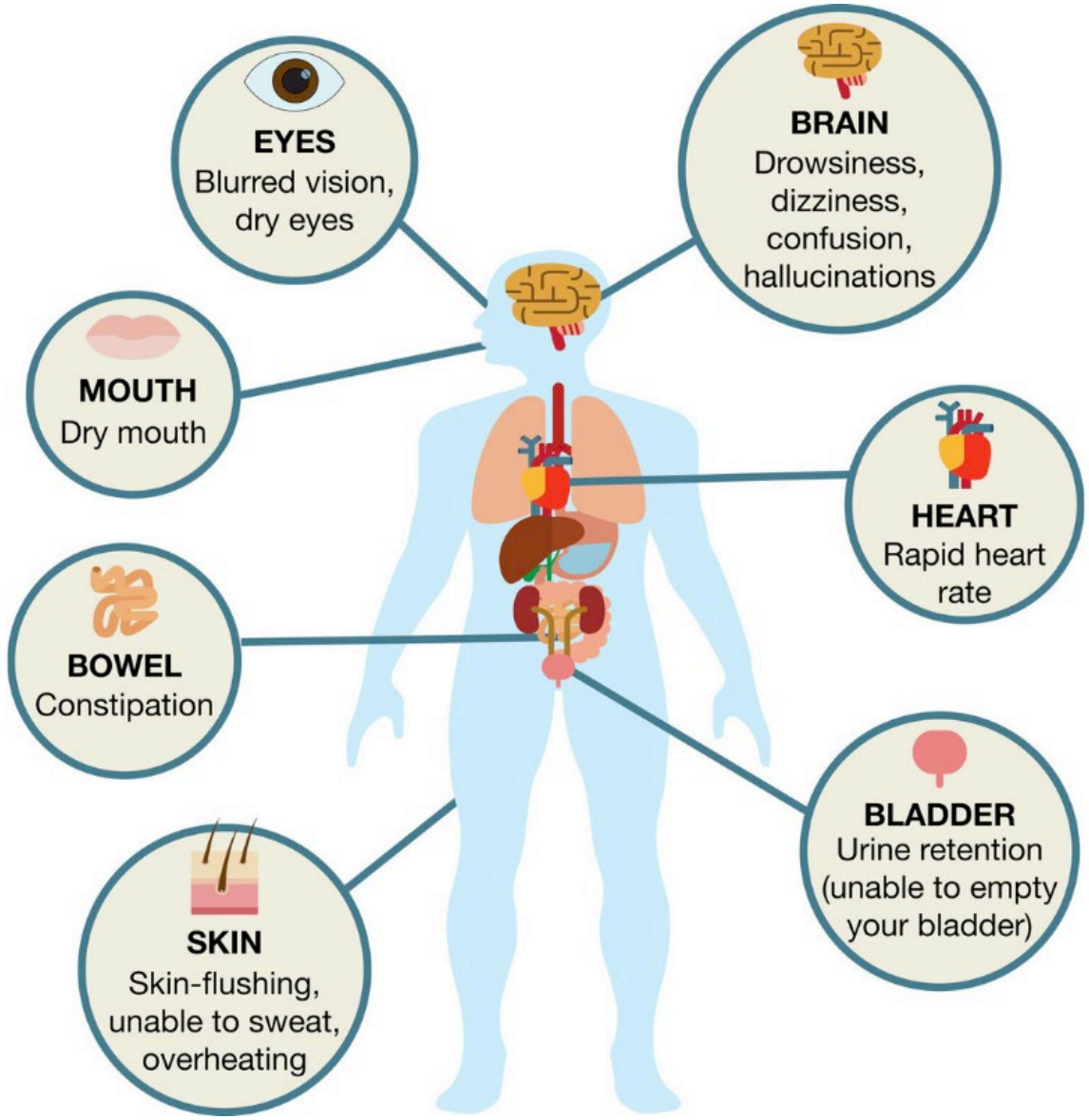
Sympathetic

Somatic



Antimuscarinics: 1st Line Medication Treatments

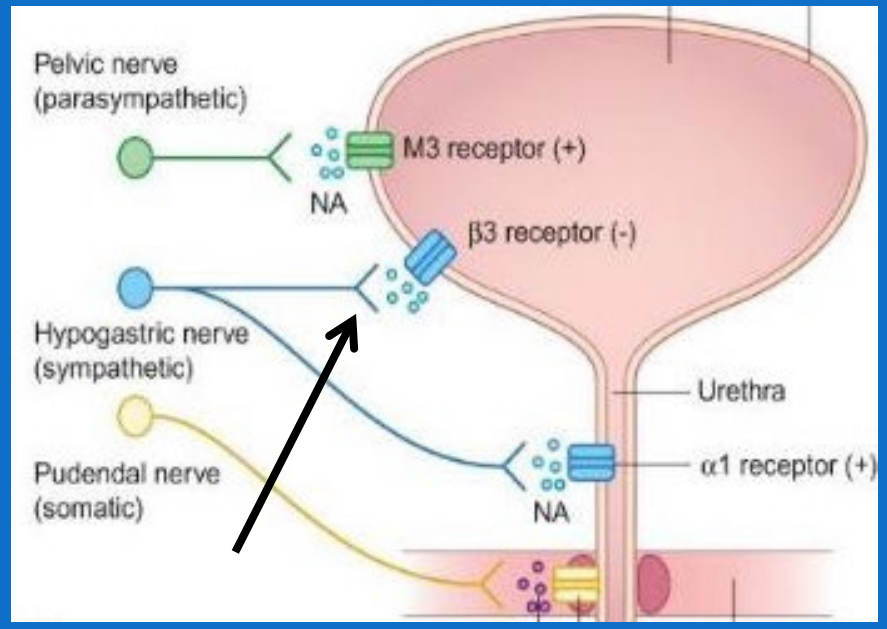
- **Benefits:** Reduce urgency & frequency
- **Risk:** May increase PVR
- **Adverse Effects:**
  - Dry mouth, blurred vision, tachycardia, constipation.
  - Potential cognitive impairment
  - Female sexual health
- **Anticholinergic Burden:**
  - Consider all other medications:
    - TCAs, Ipratropium, Tiotropium



Generic Name	Trade Name	Dose (mg)	Frequency	Receptor Activity	Notes
Antimuscarinics (Anticholinergics)					
Oxybutynin (ER)	Ditropan XL	5, 10, 15	once daily	Nonselective	High risk of crossing blood brain barrier (BBB)
Tolterodine tartrate	Detrol-LA	2, 4	once daily	Nonselective	
Fesoterodine fumarate	Toviaz	4, 8	once daily	Nonselective	Enantiomer of tolterodine
Solifenacin succinate	VESIcare	5, 10	once daily	Selective M2 & M3	
Trospium chloride	Sanctura Sanctura XR	20mg tab 60mg cap	twice daily once daily	Nonselective	Quaternary amine, theoretically does not cross BBB 20mg tablet can be crushed
Darifenacin (ER)	Enablex	15, 30	once daily	Selective M3	Highest incidence of constipation

Antimuscarinics: Treatment for Detrusor Overactivity

Beta-3 Agonists -- Another Mechanism of Action



- **Names**: Mirabegron (Myrbetriq), Vibegron (Gemtesa).
- **MOA**: Activates Beta-3 adrenergic receptors.
  - Relaxes detrusor, enhances bladder capacity
- **Potential SEs**: HTN (7-11%).
- **Advantages**: Fewer SEs, better safety improved compliance over anticholinergics.
  - Studies show lower dementia risk compared to anticholinergics.

Patient Update

- 3 months later, daytime symptoms improved;
- Nocturia persists (2-3X/night).

Desmopressin for Nocturia Management

Next Steps:

- Baseline sodium (Na+)
- Consider **desmopressin**, 10mcg intranasal
- Regular Na+ monitoring with PCP

Welk, et al. BJU international, 2020
Batla, A. et al Curr. Treat. Options Neuro., 2016)

Desmopressin for Nocturia Management

Desmopressin:

- Synthetic analog of arginine vasopressin.
- Reduces urine production by enhancing fluid reabsorption.
- Effective for nocturia, nocturnal polyuria, and nocturnal enuresis.

Use in Neurological Disorders

- Studied in Parkinsonism: PD and MSA. Limited data on long-term outcomes.

Side Effects:

- Common: Headache.
- Significant: Hyponatremia, especially in patients >65 years.

Welk, et al. BJU international, 2020

Batla, A. et al Curr. Treat. Options Neuro., 2016)

Case Summary: Treatment & Management

- Patient was started on mirabegron 50mg daily
- After continued nocturia, he started intranasal desmopressin, 10mcg nightly

Case 3

Patient with Cauda Equina Syndrome

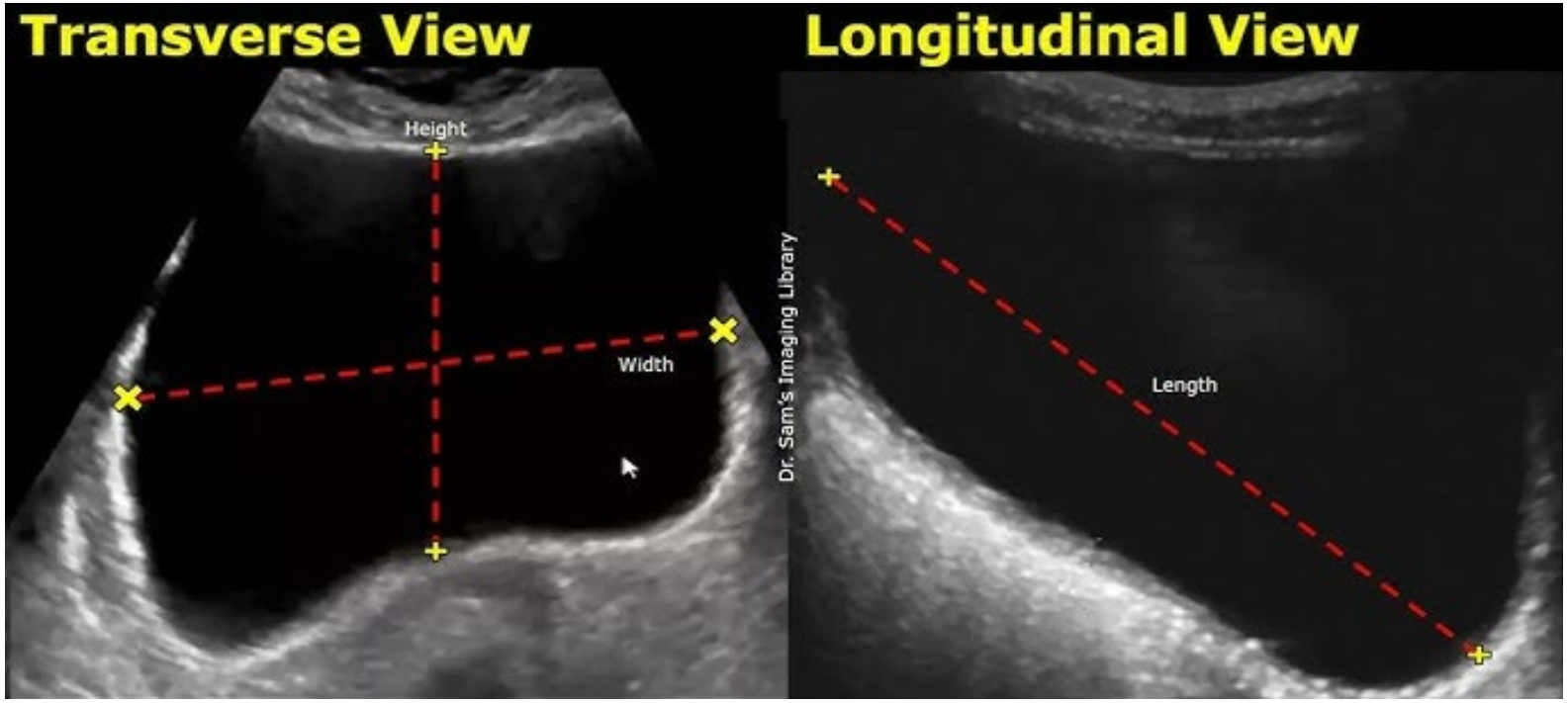
Case 3 – Cauda Equina

- 59F Severe lower back pain
- Loss of feeling between legs
- Genital numbness
- Difficulty initiating urination, Loss of sensation when passing urine
- Decreased clitoral sensation, loss of libido, pain with intercourse

Case 3 – Cauda Equina

Storage	Voiding
Bladder sensations: No	How voiding is initiated: **Unable to to start a stream or keep it flowing**
Urgency: No	Abdominal straining when voiding: **Yes**
Daytime frequency: 6x	Hesitancy: **Yes**
Nocturia: No	Quality of stream: **Interrupted voiding**
Urinary incontinence: No	Dysuria: No
	Sensation of incomplete bladder emptying after the void: **Yes**
	Double voiding**: Yes, a very slow urine stream**

Patient case study 3



PVR	Cauda equina syndrome
<200 mL	98% negative predictive value
≥200 mL	Increases the odds by 20-fold

PVR = 700 mL

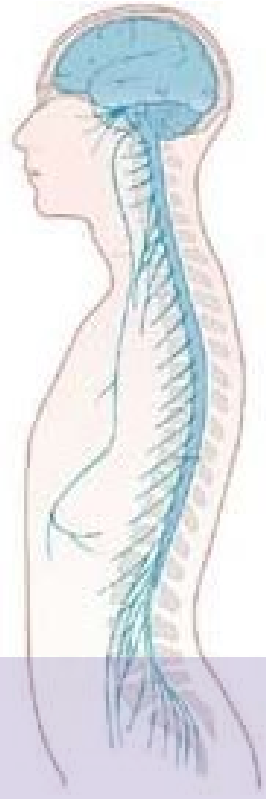
Venkatesan M, Spine. 2019

Signs & Symptoms

- **Voiding** problems: Hesitancy, straining, slow stream, double voiding
- PVR volumes: high
- Detrusor: hypoactive or atonic
- Urethral tone: normal or hypoactive
- Alterations in erectile function may have reflexogenic erections

Primary goals:

- Protect the upper urinary tract from damage
- Improve the patient's quality of life



Sacral & Infrasacral

Treatment and Management

Sacral & Infrasacral Leisons

Types of Catheters

Clean Intermittent Catheterization (CIC)

- 1st choice for neurogenic bladder patients with retention or inability to adequately drain bladder

Indwelling Catheters

- **Foley:** Only use when no other reasonable choice and CIC is not possible
- **Suprapubic:** Generally preferred when long-term use is necessary. Less urethral irritation & discomfort, avoids ventral penile erosions, easier to change, allows for use of larger-sized catheters

Long-term use should be avoided whenever possible

Nicolle, L et al 2014

Sex Differences: Self/Indwelling Catheterization

Male

- Easy access to urethra
- Convenience of urinal at bedside, promoting independence
- Non-invasive option for condom catheter

Female

- Greater challenges in accessing urethra, especially if wheelchair-bound
- No reliable external collection device
- Consequently, more likely to resort to indwelling catheters

Patient Update Case study 3

- The patient underwent surgery and her urinary symptoms resolved
- Clitoral sensation has improved but, loss of libido, pain with intercourse persist

Neurogenic Sexual Dysfunction

1°, 2°, 3° Factors related to sexual dysfunction

Ask individuals with neurological diseases about sexual problems *regularly*, explore multidimensional contributing factors

	Definition	Symptoms
Primary	Neurologic changes that directly affect sexual feelings and/or response	Impaired genital sensation, decreased libido,
Secondary	Related physical changes that affect the sexual response indirectly	Fatigue, muscle tightness, weakness, spasms, bladder and bowel dysfunction, incoordination side effects from medications, cognitive difficulties, numbness, or pain in non-genital areas
Tertiary	Psychological, emotional, social, and cultural aspects that impact sexuality	Changes in self-image, mood or body image, depression, and anger, feeling less confident about one's sexuality

Foley et al, 2014

Sexual Function & Satisfaction May be Linked to Other Symptoms in People with MS:

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Sexual problems in MS: Sex differences and their impact on quality of life

T.B. Kaplan [a,b,*], T. Feldman [a,c], B. Healey [a,b], M. Behn [b], B. Glanz [a,b], T. Chitnis [a,b]

Sexual Function and Satisfaction in 702 PwMS

- 37.7% reported low sexual function; 44.7% reported low satisfaction
- **Influencing Factors:**
- Age and disease duration impact sexual function and satisfaction in both males and females.
- All QOL domains—ex: pain, energy, physical health, social functioning, emotional well-being—associated with sexual function and satisfaction.
- **Sex Differences:**
- Males: greater association low function with emotional factors, health perception
- Females: greater association low function with disability and satisfaction with fatigue.

Commonly Used Drugs & Effects on Sexual Function

Review

Sexual dysfunction and commonly used drugs in neurology

Maya Behn,[1] Jane Kielhofner,[1] Jalesh N Panicker ,[2] Tamara B Kaplan [1,3]

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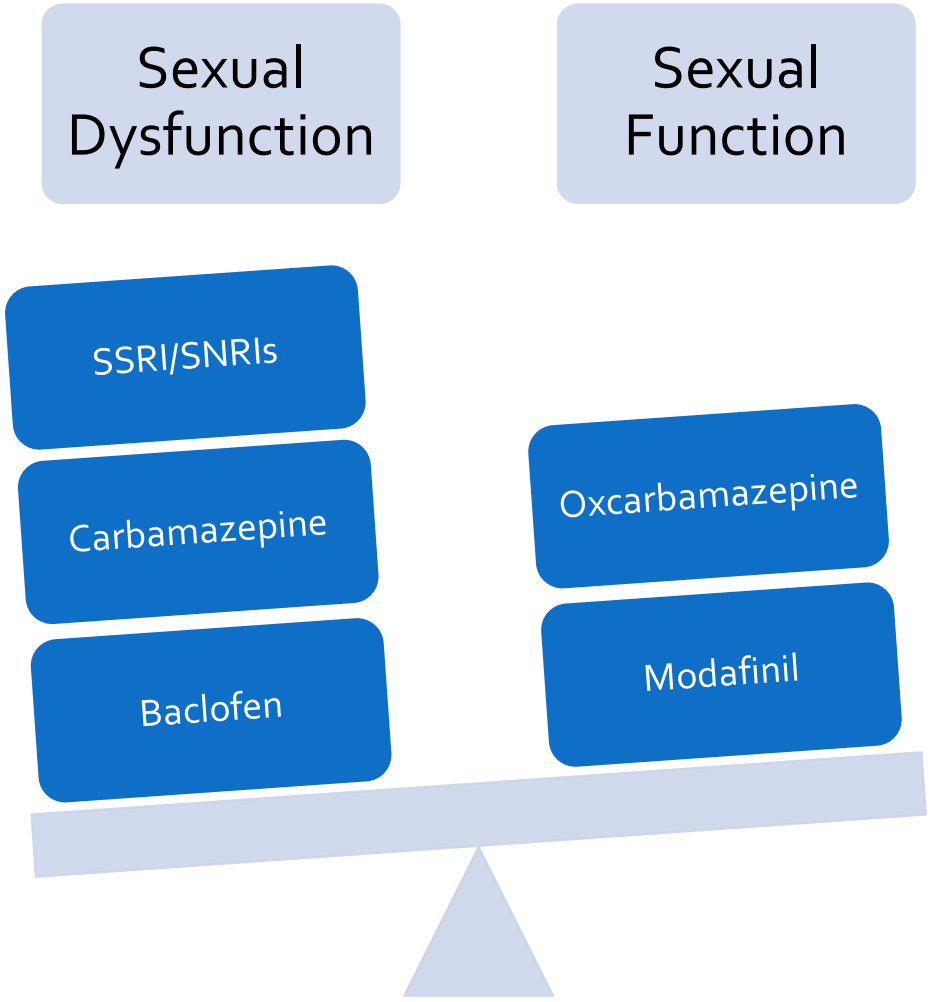
ABSTRACT

Sexual dysfunction is common in men and women with neurological diseases. Medications used in neurology can cause sexual dysfunction independently of the disease process and this sexual dysfunction secondary to medications, especially as it is potentially reversible. Drug classes commonly used in practice, including antidepressants, anti-seizure medications, stimulants, muscle

Commonly Used Drugs & Effects on Sexual Function



Behn, M., Kielhofner, J. Panicker, J. Kaplan, T, Pract. Neuro. 2024

Treatment Options for Female SD and Levels of Evidence

Difficult to use same rating system to grade psychological and pharmacologic studies

BUT lots of Level 1 & 2 evidence

Table 1. Evaluation of treatment interventions for HSDD, FSAD, and FOD

Type of intervention	Level of evidence
Psychological interventions for HSDD	
Sex therapy (sensate focus)	2*
CBT	2*
Mindfulness + CBT	2*
Pharmacologic interventions for HSDD	
Flibanserin	1
Bremelanotide	1
Testosterone therapy	1
Bupropion	2
Buspirone	2
Lybrido/Lybridos	2
Psychological interventions for FSAD	
Mindfulness + CBT	2*
Pharmacologic interventions for FSAD	
Tibolone	2
Bupropion	2†
Testosterone therapy	1
PDE5i in well-established medical conditions interfering with genital neurovascular substrates	2
Psychological interventions for FOD	
Directed masturbation	2*

Kingsberg et al., 2017

Pharmacologic Therapy for Female SD

FDA Approved	• Flibanserin (2015) • Bremelanotide (2019)
Off-Label Use	• Bupropion • Trazodone • Busprione
Possible?	• PDE5 Inhibitors: Sildenafil

Case Summary: Treatment & Management

- Sertraline was switched to bupropion
- Water-based lubricants were recommended, and dyspareunia improved

Stay Tuned…

- **European Academy of Neurology (EAN)/ European Federation of Autonomic Societies (EFAS)/ International Neurourology Society (INUS):**
- **Guidelines for practicing neurologists on the assessment and treatment of bladder and sexual symptoms in neurological patients (NEUROGED guidelines)**

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Thank you!

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