My Birdsongs in Clinical Neurology

Sarosh M Katrak

Foreword
Bhim Sen Singhal

JAYPEE

Contents

CHAPTER 16

A Simplified Understanding of the Neurogenic Bladder

One of the "blind spots" that I had in neurology was the understanding of the neurogenic bladder. Therefore, in May 2020, I made a concerted effort to understand the function of the urinary bladder in health and disease. The best way for me is to prepare a teaching power-point lecture. Only if I understand the working of the urinary bladder could I impart it to the students. In this chapter, I have drawn heavily from the publications of Professor Claire Fowler and her team from the Uro-Neurology Unit at the National Hospital of Neurology and Neurosurgery, University College London, Queen's Square, London, UK.

Simply put, the main function of the bladder is storage of urine and voiding. If one takes 2–3 minutes to void and do so four to five times a day, depending on the weather and hydration, over 95% of our lifetime, the bladder serves to store urine. The bladder cannot store urine indefinitely and at some stage there is a "phasic switching" from storage to voiding. This switch is under voluntary control: A unique feature of the bladder which sets it apart from the other autonomically controlled organs like the heart and blood vessels. During storage, the detrusor is relaxed and the sphincters are contracted and during voiding, the reverse happens, i.e., the detrusor contracts and the sphincters relax. This voluntary switch is controlled by a complex neural network involving higher cortical centers in the forebrain and certain centers in the pons. Thus, the term "neurogenic bladder" denotes lower urinary tract (LUT) dysfunction caused by malfunctioning of these "switching control centers," besides disorders involving the spinal cord, cauda equina, and peripheral innervation of the bladder.

Autonomic Innervation of the Bladder (Fig. 16.1)

The sympathetic innervation arises from T11 to L2 and via the inferior mesenteric and superior hypogastric plexus forms the hypogastric nerve. β-adrenergic receptors are inhibitory to the detrusor and α-1 adrenergic receptors are excitatory to the internal sphincter (IS).

The parasympathetic innervation arises from S2 to S4 and via the pelvic plexus forms the pelvic nerves, which innervate the detrusor. The M3

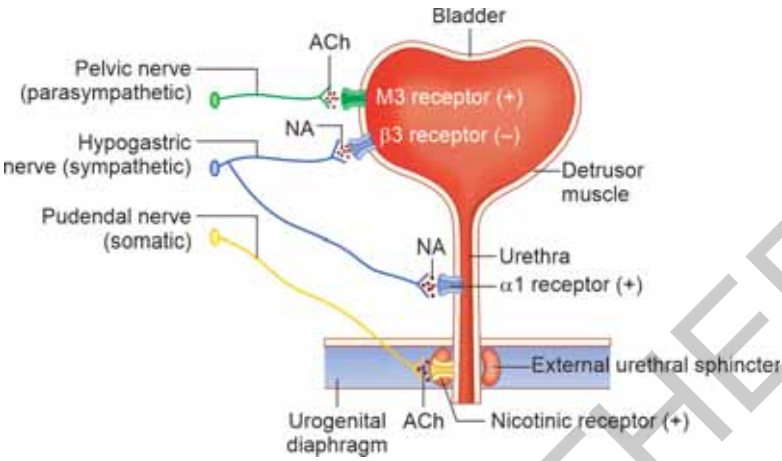


FIG. 16.1: Autonomic and somatic innervations of the bladder.
[ACh: acetylcholine; α1: adrenergic receptor; β3: adrenergic receptors; M3: muscarinic 3 cholinergic receptors; NA: noradrenaline; (+): excitatory; (-): inhibitory]

acetylcholine receptors are excitatory to the detrusor. During voiding, there is increased parasympathetic tone, with contraction of the detrusor and reciprocal relaxation of the IS because of suppressed sympathetic tone.

The somatic innervation arises from S2 to S4 and forms the pudendal nerve which innervates the striated fibers of the external sphincter. Acetylcholine-N receptors are excitatory to the external sphincter.

Afferent Innervation

The sensation of filling is conveyed by the Aδ fibers, via the hypogastric (body and bladder neck), pelvic (only body), and pudendal (urethra) nerves. These afferent impulses ascend and via the dorsal root ganglion of T11-L2 and S2-S4 enter the spinal cord and project directly to the midbrain periaqueductal gray (PAG).

As mentioned earlier, bladder filling is not indefinite; the bladder must empty at some stage. This "switching" is under voluntary control. This voluntary switching is dependent on two aspects: Mechanical and social.

Mechanical aspect: As the bladder fills, the Aδ fiber-mediated afferent signals increase in frequency and intensity. The individual gets an initial sensation of filling and, with time, a sensation to void. The latter then becomes a strong sensation to void and if appropriate circumstances are not prevalent, it can lead to urge incontinence, particularly in the elderly. Thus, the first aspect of voluntary switching is dependent on the amount of urine in the bladder—is there enough urine in the bladder to void!

Social aspect: As the individual gets a strong sensation to void, the social aspect kicks in. Simply put, is it socially appropriate to void? Is there a toilet

nearby and is it vacant? I am very fond of a saying, "How long a minute is, depends on which side of the bathroom door you are on". This aspect of social appropriateness was beautifully portrayed by Peter Sellers in the film "The Party". Lastly, in countries where open air voiding is prevalent, a "safe" situation may also come into contention.

This mechanical and social appropriateness is very succinctly termed "safe-to-void" or "unsafe-to-void" by the uro-neurology group, Queen's Square, and is governed by three important areas—the midbrain PAG, the pontine micturition center (PMC), and several areas in the forebrain, which I like to collectively call the higher neural control of micturition (HNC).

The Midbrain Periaqueductal Grey

The midbrain PAG is the rostral terminus of the afferent signals of bladder filling from the Aδ fibers. The PAG constantly distributes the frequency and intensity of these signals to several areas in the forebrain. There are feedback signals from these areas to the PAG, regarding appropriateness to void. The PAG in turn has a tonic suppressive effect on the PMC and based on inputs from the HNC either continues this tonic suppression or releases the PMC from it.

Pontine Micturition Center

Functional magnetic resonance imaging (MRI) studies have identified a medial and a lateral pontine PMC (mPMC and ltPMC). Activation of the mPMC promotes voiding by sharply increasing the intravesicular pressure and relaxing the sphincters. On the other hand, activation of the ltPMC promotes continence by increasing the contraction of the sphincters. The activation of either the medial or the lateral PMC is through signals received from the PAG as the PMC has no direct afferents from the bladder.

Higher Neural Control of Micturition

In the forebrain, there are many areas involved in the HNC of micturition. Collectively, they are responsible for the voluntary switching from storage to voiding. In each individual, there is a certain "default" setting for voiding. The main question is, "when to switch?" The centers in the forebrain collate the data provided by the PAG and answer this question! The main areas involved in the HNC of micturition are the dorsal anterior cingulate gyrus (dACC) and the insula in conjunction with the lateral prefrontal cortex (ltPFC) and the medial prefontal cortex (mPFC). These areas do not function in isolation but interact with each other and receive inputs from the supplementary motor area, parahippocampal gyrus, and hypothalamus.

The dACC is the so-called autonomic motor cortex. It generates the desire to void and the reaction to it, i.e., to postpone voiding or not. It can judge the emotional appropriateness, i.e., whether there is a subtle difference between "a strong desire to void" and "urgency." The dACC has the capacity to differentiate this subtle difference in order to postpone or initiate voiding. The insula and the ltPFC are the so-called autonomic sensory cortex. The

insula interacts with the ltPFC and judges the qualitative value of bladder filling: Is the sensation comfortable, tolerable, or uncomfortable? The mPFC is the seat for appropriate social behavior and plans the appropriateness of micturition. It is involved when a voluntary decision about voiding is required and therefore has a strong direct influence on the PAG either maintaining or deactivating the tonic suppression.

Hence, the sequence of events in normal continence and voiding is shown in **Figures 16.2 and 16.3**.

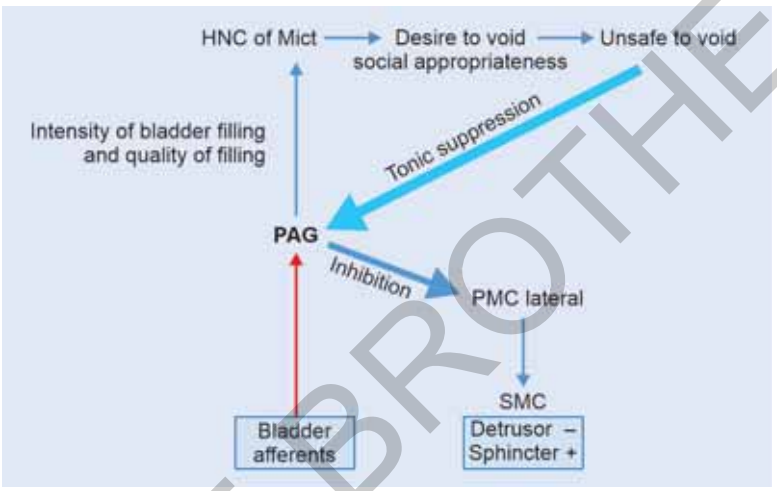


FIG.16.2: Circuit to maintain continence.
(HNC of Mict: higher neural control of micturition; PAG: periaqueductal gray; PMC: pontine micturition center; SMC: sacral micturition center; +: contracting; –: relaxation)

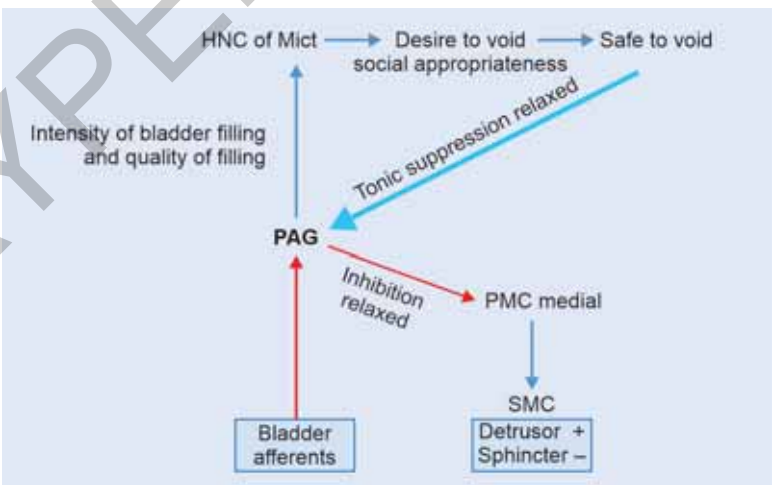


FIG. 16.3: Circuit for voluntary switch to voiding.
(HNC of Mict: higher neural control of micturition; PAG: periaqueductal gray; PMC: pontine micturition center; SMC: sacral micturition center; +: contracting; –: relaxation)

Thus, LUT dysfunction can occur at:

- *Suprapontine level*: Frontal lobe, basal ganglia, and midbrain level
- *Pontine level*: Rare
- *Spinal cord level*: Particularly lumbosacral cord
- *Cauda equina level*: Very early LUT dysfunction
- *Peripheral innervation*: Uncommon

Symptoms and signs will depend on the site of involvement and may involve purely upper motor neuron (UMN) signs (suprapontine problems), pure lower motor neuron signs (cauda equina/peripheral innervation), or a combination of both (lesions involving lower spinal cord and cauda equina). Hence, the clinical examination should be directed at establishing the level of the lesion in the nervous system. Do not rely too much on bladder symptoms. Frequency, urgency, or urge incontinence can occur in any lesion above the lumbosacral spinal cord. However, in a spinal cord lesion, the patient has incontinence with awareness whereas in the late stages of dementia, the patient has incontinence without awareness. Some patients with cauda equina lesions and secondary urinary tract infection (UTI) may complain of urgency in the early stages.

One should, however, rely on a combination of symptoms and signs. In a spinal cord lesion, one can get a combination of LUT and sexual dysfunction, whereas with an enlarged prostate there will be only LUT dysfunction. I may stress here that a history of sexual dysfunction is grossly neglected in our clinical practice, especially in women.

Another two aspects of an extended clinical evaluation of a patient with a neurogenic bladder are worth mentioning:

Postvoid residue (PVR): The history of incomplete voiding is usually not a reliable index of a PVR. The PVR can be reliably assessed on the ultrasound sonography (USG) or a quick "in-and-out-catheterization." Any PVR of >100 mL has the potential of a UTI and the patient should be advised clean intermittent self-catheterization (CISC). This is usually the case in patients with infrasacral lesions. Patients with spinal cord problems have a PVR but usually <100 mL. They may be monitored closely on anticholinergic drugs. Patients with suprapontine lesions are incontinent without any PVR.

Neurological per-rectal (PR) examination: The anal tone is a good reflection of the state of the external sphincter as they share a common motor innervation: S2 to S4 and the pudendal nerve. However, the neurological PR examination should only be performed in cases of cauda equina or peripheral innervation problems. After inserting your index finger in the anal canal, ask the patient, "what would you do if you had a strong urge to pass stool and you did not want to dirty your clothes?" He or she will contact the anal sphincter. Judge the "power" around your index finger. Normally, it is a tight squeeze and is easily differentiated from a weak anal sphincter. If there is total denervation, the anal sphincter is patulous and there is no "resistance" to the entry of your index finger.

The most common suprapontine lesions are (1) frontal lobe lesions, (2) multiple system atrophy-parkinsonian type (MSA-P), and (3) Parkinson's disease (PD).

Frontal lobe lesions: In such lesions, the bladder dysfunction is because of lack of inhibition of the PAG and thus the PMC. There is socially inappropriate voiding with associated neuropsychiatric symptoms and signs. In the early stages, there maybe awareness of incontinence but in the late stages the patient is not aware. As mentioned earlier, there is no PVR. The main etiologies are traumatic brain injury (TBI), strokes, dementias [Alzheimer's disease (AD) and frontotemporal dementia (FTD)], normal pressure hydrocephalus (NPH), advanced multiple sclerosis (MS), and frontal lobe gliomas.

MSA-P: The earliest features are erectile dysfunction followed later by urgency and urge incontinence. If both occur early, the prognosis is poor. Initially, there is detrusor overactivity but as the disease progresses there is voiding dysfunction with detrusor inactivity. Thus, there is incomplete voiding and an increasing PVR, a feature characteristic of MSA-P. Thus, follow-up USG assessment of PVR helps to differentiate it from PD. In the late stages, because of the involvement of the sympathetic innervation, there is incontinence with a lax IS. The external sphincter is also involved because of loss of neurons in Onuf's nucleus in the sacral spinal cord.

PD: In PD, the main autonomic problem is constipation. Urinary complaints do occur but late in the disease. There is detrusor overactivity with nocturia and urgency in the majority of patients. Unlike MSA-P, the PVR is typically low.

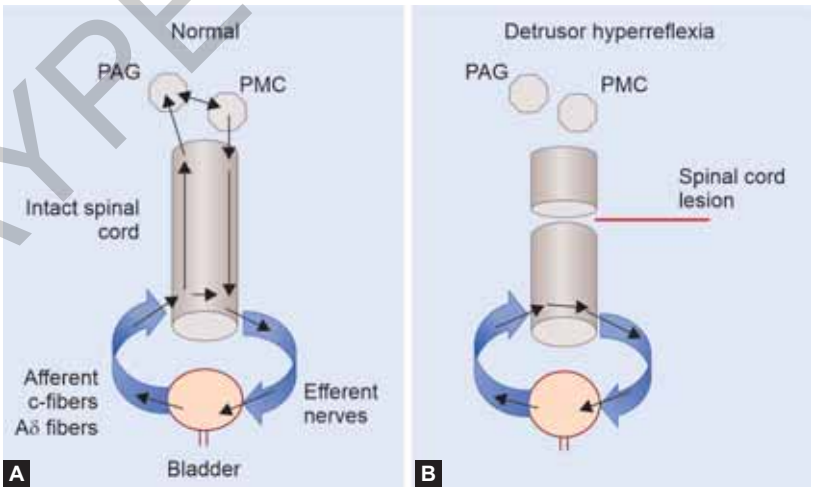
Pontine lesions: As brainstem lesions produce a lot of signs, isolated bladder dysfunction in pontine lesions is very uncommon. Rarely discreet lesions in the tectal area of the midbrain may produce bladder dysfunction by affecting the PAG.

Spinal cord lesions: In the spinal cord, bladder dysfunction is early and more severe in lesions of the lumbosacral area. In the thoracic area, symptoms occur pari passu with the paralytic signs. In the high cervical area, usually compression, I have rarely seen bladder involvement. At the JJ Hospital, we had many patients who were quadriparetic from atlantoaxial dislocation, but none of them had bladder involvement.

Bladder involvement is more common in acute involvements of the spinal cord, be it trauma or acute compression from a pathological vertebral collapse. Initially, there is spinal shock with retention of urine which will need catheterization. The retention should be detected early. I have seen many patients with an overdistended bladder and overflow incontinence. On catheterization, between 700 and 1,000 cc of urine is drained. The net result is that the detrusor is overstretched and on recovery, there is detrusor underactivity. A rule of the thumb states that with 1 hour of retention, the

bladder will take 24 hours to recover and beyond a certain point in time, it is unlikely that there will be any recovery. Hence, in the acute stages, palpating or percussing (unfortunately a lost art) for a full bladder is imperative. With a severe lesion, voiding becomes a segmental reflex—the so-called automatic bladder **(Figs. 16.4A and B)**. In health, unmyelinated afferent c-fibers are unimportant in generating detrusor contractions, as the Aδ fibers directly convey the relevant information to the PAG. With a severe spinal cord lesion, the circuit involving Aδ fibers is nonfunctional; so the c-fibers become the main afferent arc for detrusor contraction. This segmental reflex gives rise to detrusor overactivity which is ill sustained and weak. Besides this, it must be noted that the PMC controls the reciprocal activity of the detrusor and sphincters. When the PMC is "disconnected", you get weak, ill-sustained detrusor activity against uncoordinated sphincters—detrusor–sphincter dyssynergia (DSD). The net result is incomplete voiding, increasing PVR, LUT infections, and intermittent increase in intravesical pressure (detrusor contraction against uncoordinated closed sphincters). This in turn increases the risk of upper UTI and renal failure. Both the detrusor overactivity and DSD correlate with the duration and extent of the pyramidal damage.

Cauda equina lesions: In a cauda equina problem, both the afferent sensory inputs and the efferent motor innervations of the bladder are involved. Urinary retention is the most common presenting symptom associated with fecal incontinence. As the sensory afferents are affected, there is no urge to urinate, and overflow incontinence follows. Spontaneous detrusor contractions are lacking, and low-level weak detrusor overactivity persists. As the sphincters are also weak, this results in constant dribbling of urine. The PVR is usually high (over 100 mL). The clinical features may vary depending



FIGS.16.4A AND B: Circuit for a segmental reflex in a suprasacral spinal cord lesion.
(PAG: periaqueductal gray; PMC: pontine micturition center)

on whether the onset is acute or gradual. If the etiology is an acute intervertebral disc prolapse or tuberculosis spinal meningitis, the patient may have acute low backache and bilateral but asymmetrical root pains. Weakness of the lower limbs is also asymmetrical and distal more than proximal. The sensory loss is usually along the posterior aspect of the thigh (S2-3) and perianal region (S3-5)—the classic saddle anesthesia. The anal sphincter tone is weak or lost, explaining the associated fecal incontinence. In males, sexual dysfunction involves erection and lack of ejaculation whereas in females, it involves absence of orgasm and vaginal lubrication.

An acute cauda equina syndrome is a medical emergency. The retention of urine should be detected early and the patient catheterized, to prevent massive retention with overflow incontinence. The next step is to establish the etiology and start appropriate therapy. If the etiology is an acute disc prolapse, emergency decompression will go a long way in improving bladder, bowel, and sexual dysfunction. For residual bladder dysfunction, CISC, three to four times a day, is preferred to avoid long-term catheterization and UTI.

Lesions of the peripheral innervation: This usually implies peripheral neuropathy. It must be remembered that the bladder innervation is over a short length of nerve fibers. Therefore, in length-dependent peripheral neuropathies, like diabetes, the bladder involvement is late with well-established symptoms and signs of a peripheral neuropathy. In diabetic bladder dysfunction, the sensory afferents are more affected, resulting in a large capacity bladder. It is not unusual to have 700 mL of urine on USG before the first urge to void occurs. Detrusor contractions do occur but are weaker than normal, resulting in a high PVR. Secondly, orthostatic hypotension and male erectile dysfunction occur earlier than bladder dysfunction. In fact, erectile dysfunction may be the presenting symptom in some cases of unsuspected diabetes.

THERAPY OF THE NEUROGENIC BLADDER

I will outline the principles of therapy together with some details of the therapy of an overactive bladder (OAB).

The main aim of therapy is to achieve urinary continence, thereby preventing UTI, preserving upper urinary tract function, and, very importantly, improving the quality of life for the individual. Therapy, in a hierarchal fashion, involves conservative measures, nonsurgical and then surgical interventions.

Conservative measures involve bladder training and pharmacotherapy. Nonsurgical interventions are intravesicular botulinum toxin injections, particularly in cases of spinal cord trauma and MS and percutaneous posterior tibial nerve stimulation. The posterior tibial nerve is the large terminal branch of the sciatic nerve with a root value of L4-5 S1-3. Lastly, surgical interventions are sacral nerve neuromodulation, bladder augmentation, anterior root stimulation, and continent/incontinent diversion.

Bladder training: This is effective in incontinence due to cognitive and motor deficits, i.e., OAB. One of the important steps is to maintain a bladder diary. This helps in establishing a realistic voiding interval and then instructing the patient in doing timed voiding. Fluid intake, reducing caffeine/alcohol, and avoiding diuretic therapy are other measures which help maintaining continence. Biofeedback pelvic floor muscle training is useful in cases of stress incontinence, particularly in multiparous females. It suppresses activity in the dACC and reduces the fear of incontinence.

Pharmacotherapy for LUT dysfunction should be individualized based on the degree of bother to the patient, medication side-effect profile, concomitant comorbidities, and current medication regimen, particularly for drugs with anticholinergic side effects.

The bladder may be OAB or underactive bladder (UAB). In OAB, the main receptors which are targeted are (1) antimuscarinic cholinergic receptors and (2) β-adrenergic receptor agonist. Other drugs that are used are imipramine, a tricyclic antidepressant medication, and the benzodiazepines (See **Fig. 16.1**, page 125).

There is no effective therapy for a UAB, but some medications have been used with limited success—muscarinic receptor agonists to increase the detrusor tone, anticholinesterase inhibitors again to increase acetylcholine levels and thereby increase detrusor tone, and α-adrenergic receptor antagonists to relax the IS **(**See **Fig. 16.1)**.

The bladder may also be involved at the level of the outlet. Decreased resistance of the outlet results in stress incontinence. This is best managed with biofeedback pelvic floor muscle training together with an α-adrenergic receptor agonist to increase the IS tone and/or β-adrenergic receptor agonist to reduce detrusor contractions and/or imipramine. Increased resistance at the outlet results in bladder outflow obstruction. This is managed by α-adrenergic receptor antagonists, to relax the IS, together with benzodiazepines, baclofen, or phosphodiesterase inhibitors.

Anticholinergic therapy for OAB **(Table 16.1)**: Anticholinergic drugs (AChD) block the muscarinic (M3) cholinergic receptors at the detrusor muscle, thus decreasing detrusor overactivity. But no drug is totally selective for the detrusor and therefore acts at other muscarinic sites to produce side effects—dry mouth and eyes, constipation, confusion in the elderly, blurred vision, somnolence, and tachycardia. The newer AChDs have similar efficacy but have a greater bladder selectivity, thereby reducing side effects. Hence, the choice of an AChD is not based on efficacy but on the side-effect profile.

Oxybutynin is considered the first-line drug because of its cost effectiveness, safety, efficacy, and tolerability in a considerable proportion of patients. Start therapy at a low dose, 2.5 mg BID, and then gradually increase the dose to a maximum of 5 mg TID if the PVR < 100 mL. Monitor the PVR every 2 weeks to judge the efficacy of therapy. Oxybutynin with bladder training results in a good outcome at the lowest possible dose. If the side effects are

TABLE 16.1: Frequently used anticholinergic drugs.

Name	Receptor selectivity	Central nervous system levels*	Other side effects
Oxybutynin	Nonselective	Mod/High	Mod/High
Tolterodine	Nonselective	Low	50% of oxybutynin
Solifenacin	M2, M3	Low	Low rate
Darifenacin	M3	Low	Low rate
Trospium	Nonselective	Very low	Low rate
Fesoterodine	Nonselective	Low	Low rate

*CNS levels reflect the drug's ability to cross the blood–brain barrier.
(M2: muscarinic 2 receptors; M3: muscarinic 3 receptors)

unmanageable, switch to a second-line drug like tolterodine and monitor the PVR. The patient may be referred for specialized care in case of failure to respond to second-line drug therapy. In spinal cord lesions with DSD, AChDs with judicious use of CISC are very effective. Before starting AChDs, it is important to document the current regimen of drugs that the patient is on, particularly for drugs with high anticholinergic action. This is essential as drug interaction may result in adverse side effects and discontinuation of anticholinergics for the OAB.

β-3 receptor agonists (BRAg) are the newer groups of drugs used for OAB—mirabegron and vibegron. β-3 receptor activation produces detrusor relaxation, thus resulting in their use for OAB. Mirabegron can be synergistically combined with Solifenacin. They produce a lesser degree of dry mouth and constipation. BRAgs must be used cautiously (mirabegron > vibegron) in patients with concomitant ischemic heart disease as their serious side effects include rise of BP, tachycardia, and atrial fibrillation. Mirabegron is contraindicated in patients with severe uncontrolled hypertension.

I hope this simplified explanation of the normal functioning of the urinary bladder helped you to understand the complex neural control involved in maintaining continence. Once that is understood, it becomes easier to understand the dysfunctions of the bladder from lesions at various levels of the neural pathways. I would like to reiterate the importance of the PVR not only in making decisions for management but also in monitoring the efficacy of drug therapy. The principles of pharmacotherapy for an OAB have been explained.

RECOMMENDED ARTICLES

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My Birdsongs in Clinical Neurology

This book is based on the clinical and teaching experiences of the author of over 50 years in the practice of neurology. It is not a complete book but should be used as a companion to larger textbooks on clinical methods in neurology. This book contains many clinical tips that will make neurological examination easier and enjoyable without losing its accuracy. He has used applied anatomical facts and at times applied physiology to explain difficult to understand findings. Professor Bhim Sen Singhal, in his foreword, has summarized the essence of the book by stating: "I thoroughly enjoyed reading this book. I have learnt a few lessons which I will make use of when seeing my patients. I strongly recommend this book, not only for postgraduate students in medicine and neurology, but also for the practicing neurologist."

Sarosh M Katrak is Professor Emeritus, Department of Neurology at the Grant Medical College and Sir JJ Group of Hospitals, and Emeritus Director, Department of Neurology at Jaslok Hospital and Research Centre, Mumbai, Maharashtra, India. He is a seasoned clinical neurologist and a much sought after teacher. He has delivered lectures and orations at national and international meetings. He delivered the Masland Oration at the World Congress of Neurology, Vienna, Austria in September 2013. He has published important scientific papers in prestigious, peer reviewed national and international journals such as Lancet, Brain and Journal of Neurological Sciences. He was the Co-Chair of the Teaching Course Committee of the World Federation of Neurology between 2014 and 2017. For his outstanding contribution to neurology education, he was awarded the Ted Munsat Award by the World Federation of Neurology in October 2019 at the World Congress of Neurology, Dubai. He is passionate about both architectural and wildlife photography as well as calligraphy.

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