INTRODUCTION

The International Continence Society (ICS) defined overactive bladder syndrome (OAB) as urinary urgency with or without urgency incontinence, often accompanied by frequency and nocturia in the absence of infection or other obvious pathology. Urinary urgency is the complaint of a sudden compelling desire to void which is difficult to defer with patients often suffering from anxiety due to fear of leakage. Urgency urinary incontinence is defined as involuntary leakage of urine, accompanied or immediately preceded by urgency ***(Abrams, 2002).***

Overactive bladder syndrome is a clinical diagnosis. On the other hand, detrusor overactivity (DO) is a urodynamic finding, characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked. These terms aren't interchangeable, as overactive bladder syndrome patients may not have detrusor activity on urodynamic testing ***(Guralnick et al., 2010)***.

The National Overactive Bladder Evaluation (NOBLE) program was developed to estimate the prevalence of OAB and its burden in the United States, assess the influence of gender on OAB and its symptoms and determine the impact of OAB on quality of life, sleep, and general mental health. More than 5,000 participants completed the study that showed an overall OAB prevalence of ~16% with no significant differences

between the two sexes. (16% in men, 16.9% in women) ***(Nitti, 2002)*.**

The study demonstrated that OAB without urgency incontinence (OAB dry) was more common in men than in women. OAB with urgency incontinence (OAB wet) increased with age in both sexes, increasing from 2% to 19% in women after the age of 44 years and from 0.3% to 9% in men with a marked increase after 64 years. While the prevalence of OAB with and without urgency incontinence in women was similar (9.3% and 7.6%), in men the prevalence of OAB wet (2.6%) was much lower than the prevalence of OAB dry (13.4%) ***(Nitti, 2002).***

The difference between males and females in urgency incontinence could be attributed to the anatomical and physiological differences in urinary continence mechanisms such as a shorter female urethra and the effect of pregnancy and vaginal delivery on the pelvic floor ***(Eapen et al., 2016)***.

It also revealed that men and women with OAB had clinically and statistically significant lower quality of life and poorer quality of sleep than did controls after adjusting for comorbid illnesses ***(Reynolds et al., 2016).***

An online survey of US women with OAB, 39 % reported that OAB interfered with daily activities, with 12% staying at home because of their symptoms; 38 % reported

decreased physical activities, while 34 % attributed weight gain to OAB because of an inability to exercise. Women with OAB were also significantly more likely than those without OAB to report disturbed sleep, decreased self-esteem, decreased sexuality, and feeling of overall declining health ***(Dmochowski et al., 2007)***.

An important public health consideration of OAB is the gap between the onset of symptoms and seeking and receiving treatment for symptoms as few individuals who have OAB seek care. In fact, OAB patients often delay seeking treatment or even discussing their symptoms with healthcare providers. A study found that women who had discussed OAB symptoms with a care provider had waited on average 3.1 years after the onset of symptoms with increased symptom severity as the driving force for patients to seek treatment ***(Wolff et al., 2014).***

OAB not only diminish overall quality of life, but also create additional health problems for patients. These include an increased risk of falls and fractures, urinary tract infections, sleep disturbances, and depression ***(Vetter et al., 2017).***

Some studies have identified urinary urgency and urgency incontinence as risk factors for recurrent falls and fractures in the elderly. A study established that the odds ratio of a hip fracture in urinary-incontinent elderly women was twice that in the general population while women suffering from urgency incontinence once weekly had a 26% greater risk

of sustaining a fall and a 34% greater risk of fracture. When incontinence occurred daily, these risks increased to 35% and 45%, respectively ***(Karabulut et al., 2018)***.

The economic burden of any disease is determined by direct costs, indirect costs, and intangible costs. Direct costs include routine care, treatment and diagnostic costs. Indirect costs are those suffered from lost wages to patients and caregivers and lost productivity as a result of morbidity. Intangible costs consist of the value of pain and the decreased quality of life associated with an illness. The total national costs of OAB in the U.S are estimated to be $12 billion with 9 billion more as an indirect cost ***(Basra et al., 2007).***

Anti muscarinic drugs represent the cornerstone of medical treatment of OAB syndrome. They offer significant improvements in patients' symptoms and quality of life. They are generally well tolerated with predictable side effects. They exert their action through inhibiting acetylcholine, which stimulates detrusor contraction via muscarinic receptors. They vary according to receptor selectivity and adverse effects ***(Kruse et al., 2012)***.

Solifenacin succinate is a once-daily, oral antimuscarinic agent with two dosage forms, 5 mg and 10 mg. It showed significant reduction in symptoms of OAB (urgency, incontinence, and frequency), and was associated with a favorable tolerability profile ***(Chapple et al., 2004)***.

AIM OF THE WORK

To determine the relation between clinical improvement and urodynamic based improvement in patients with overactive bladder syndrome receiving anticholinergic drugs.

Chapter One

NEUROPHYSIOLOGY OF LOWER URINARY TRACT

The urinary bladder collaborate with the urethra and pelvic floor muscles (lower urinary tract) to perform its two main functions, low pressure urinary storage and periodic voluntary voiding. Alternation between these actions requires coordination between many components including central nervous system, autonomic nervous system, detrusor smooth muscles, urothelium, external urethral sphincter and pelvic floor muscles. Failure of this coordination may lead to multiple symptoms such as urinary retention, incomplete voiding, incontinence or overactive bladder syndrome ***(Dasgupta et al., 2007)***.

Lower urinary tract is controlled by neural inputs, circulating hormones and local mediators. The neural control is derived from parasympathetic, sympathetic and somatic nervous systems each carrying afferent and efferent impulses ***(De Groat et al., 2015).***

Afferent innervation of lower urinary tract

Afferent innervation of lower urinary tract is supplied by the autonomic and somatic nervous systems through pelvic, hypogastric and pudendal nerves to lumbosacral dorsal root ganglia. The bladder neck and proximal urethra have the largest afferent supply within the lower urinary tract. Pelvic nerve

afferents consist of myelinated A delta fibers and unmyelinated C fibers ***(Birder et al., 2010)***.

A delta fibers are sensitive to passive distension of the bladder with threshold 5 -15 mm H2O (intravesical pressure of first sensation in normal urodynamic studies) while C fibers are usually silent. During pathological conditions (i.e. inflammation, neuropathy) there is recruitment of C fibers that may be the cause of urgency and bladder pain. Sensations are conveyed from afferent neurons within the spinal cord to periaqueductal grey and pontine micturition center ***(De Groat et al., 2009).***

Afferent impulses are modulated by multiple local factors including nitric oxide, purines and cytokines. They act by either rendering afferent nerves hypersensitive i.e. increasing their firing rate and amplitude or inhibiting them ***(Drake et al., 2010)***.

Efferent innervation of lower urinary tract

1- Parasympathetic innervation

Preganglionic parasympathetic innervation to lower urinary tract arises from sacral spinal cord (S2-S4). Synapsis with postganglionic neurons occurs at the pelvic plexus, ganglia overlying the urinary bladder or intramural ganglia. Intra ganglionic transmission occurs through Acetyl choline acting on nicotinic receptors. Ganglionic transmission can be modulated by presynaptic adrenergic, muscarinic and purinergic receptors ***(Clemens, 2010).***

Post ganglionic parasympathetic supply to the urinary bladder results in detrusor smooth muscles contraction through the action of Acetyl choline on muscarinic receptors and bladder neck and urethral smooth muscles relaxation ***(Fowler et al., 2008).***

2- Sympathetic innervation

Sympathetic innervation to lower urinary tract originates at the thoraco lumbar level of the spinal cord (T10-L2). Postganglionic sympathetic fibers travel through hypogastric and pelvic nerves after relaying in inferior mesenteric ganglia and paravertebral sympathetic chain ganglia respectively. Sympathetic innervation to the lower urinary tract results in detrusor relaxation by action of noradrenaline on beta three receptors and bladder neck and urethral smooth muscles contraction. It also inhibits parasympathetic transmission at spinal level ***(Chancellor et al., 2004).***

Male bladder neck muscles, unlike female muscles, are richly innervated by adrenergic fibers which upon stimulation lead to closure of the bladder neck. This mechanism can maintain continence in patients with injured striated sphincter ***(Gosling et al., 1977)***.

3– Somatic innervation

Somatic innervation to rhabdo sphincter originates from Onuf's nucleus (ventral horns of sacral spinal levels S2 – S4). It has excitatory effect on external urethral sphincter through the action of Acetyl choline on nicotinic receptors ***(De Groat et al., 2015).***

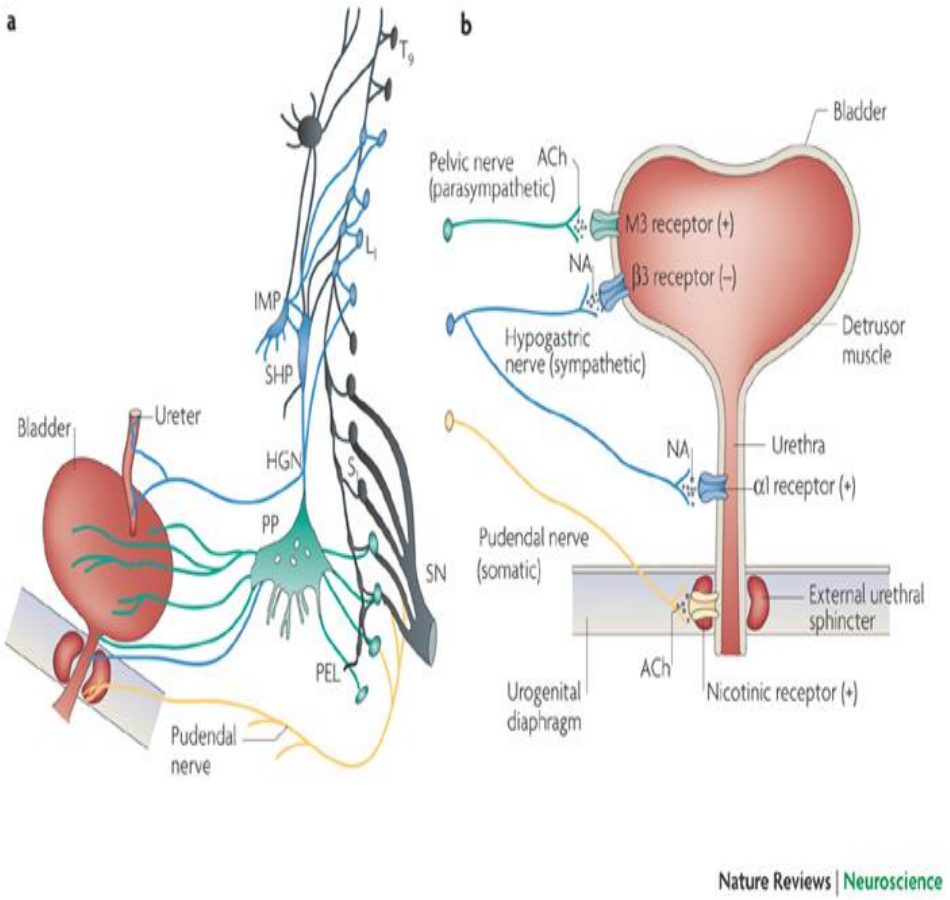

Figure (1): Efferent innervation of the lower urinary tract adapted from neural control of micturition by De Groat et al., 2015.Fig.A Sympathetic fibers (shown in blue) originate in the T11–L2 segments, Parasympathetic preganglionic fibers (shown in green) arise from the S2–S4 spinal segments, Somatic motor nerves (shown in yellow) arise from S2–S4 segments. Fig.B Parasympathetic postganglionic axons in the pelvic nerve release acetylcholine (ACh), which produces a bladder contraction by stimulating M_3 muscarinic receptors in the bladder smooth muscle. Sympathetic postganglionic neurons release noradrenaline (NA), which activates β_3 adrenergic receptors to relax bladder smooth muscle and activates α_1 adrenergic receptors to contract urethral smooth muscle. Somatic axons in the pudendal nerve also release ACH, which produces a contraction of the external sphincter striated muscle by activating nicotinic cholinergic receptors. SHP, superior hypogastric plexus; SN, sciatic nerve; IMP, inferior mesenteric plexus; SHP, superior hypogastric plexus;HGN, hypogastric nerve; PP, pelvic plexus; PEL, pelvic nerves.

Storage phase

There is no or minimal increase in intravesical pressure during storage phase until voiding threshold is reached. This vesical compliance is due to intrinsic characteristics of the urinary bladder smooth muscles and stroma as well as autonomic and somatic innervation. The vesical stroma contains collagen, elastin, and proteoglycans which play a major role on bladder compliance. Also the bladder smooth muscles have a broad length-tension relationship, allowing tension to be developed over a large range of resting muscle lengths ***(Wyndaele, 2011).***

Sympathetic stimulation results in closure of urethral outlet and inhibition of vesical contractions, while inhibition of parasympathetic efferents decreases detrusor contractions. During filling, there is increase in the activity of the external urethral sphincter that could be detected by EMG (guarding reflex). This reflex help in maintaining continence during filling and is caused by stimulation of pudendal nerve by bladder afferent impulses ***(Brucker et al., 2012).***

Voluntary contractions of pelvic floor muscles lead to inhibition of micturition through central inhibitory impulses. Patients are advised to do such contractions as a method of urge control ***(Fowler, 2008).***

Voiding phase

When the volume of urine reaches micturition threshold and social circumstances are appropriate, increased rate and amplitude of afferent impulses travelling from the urinary bladder to cerebral centers stimulate efferent parasympathetic firing under cerebral control with inhibition of both sympathetic and somatic outflow resulting in relaxation of urethral sphincter followed by detrusor contraction and urinary flow. Passage of urine through urethra facilitates detrusor contractions by stimulating pudendal nerve afferents that facilitate parasympathetic outflow ***(De Groat et al., 2009).***

Relaxation of urethral smooth muscles during voiding is caused by nitric oxide due to parasympathetic activation while relaxation of external striated urethral sphincter during detrusor contraction is partially dependent on supraspinal control, that's why patients with spinal cord injury suffer from detrusor sphincter dyssynergia ***(Drake et al., 2010).***

Supraspinal control

Pontine micturition center or Barrington nucleus, first described by Barrington in 1925, is a group of neuronal cell bodies in the dorsal aspect of the pons. It orchestrates the act of voiding by coordinating detrusor contraction with sphincter relaxation ***(Fowler, 2008).***

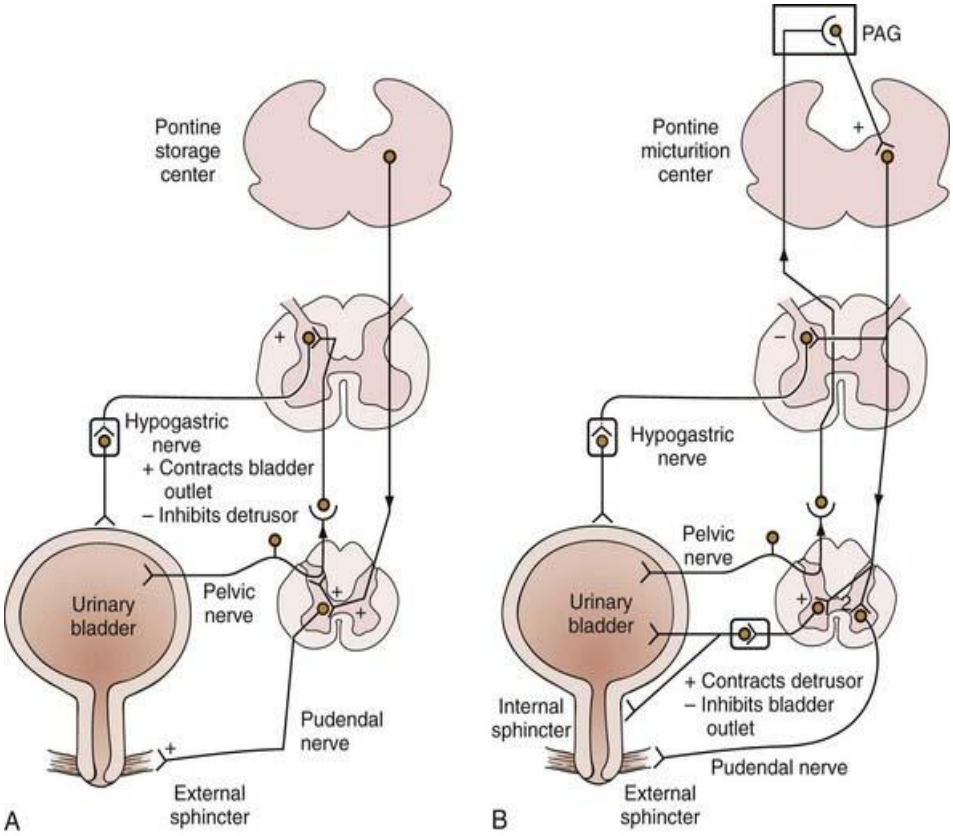

Figure (2): Neural control over filling and micturition, adapted from anatomy and physiology of the urinary bladder by Baptiste et al., 2009. Fig.A During storage of urine, distention of the bladder results in low-level afferent firing, which stimulates the sympathetic outflow to the bladder and the pudendal outflow to the external urethral sphincter. These represent guarding reflexes, which promote continence. Sympathetic firing also inhibits contraction of the detrusor muscle. Fig. B During micturition, intense bladder-afferent firing in the pelvic nerve activates spinal reflexes that pass through the pontine micturition center. This stimulates the parasympathetic outflow to the bladder and to the urethral smooth muscle and inhibits the sympathetic and pudendal outflow to the urethral outlet. PAG: periaqueductal grey.

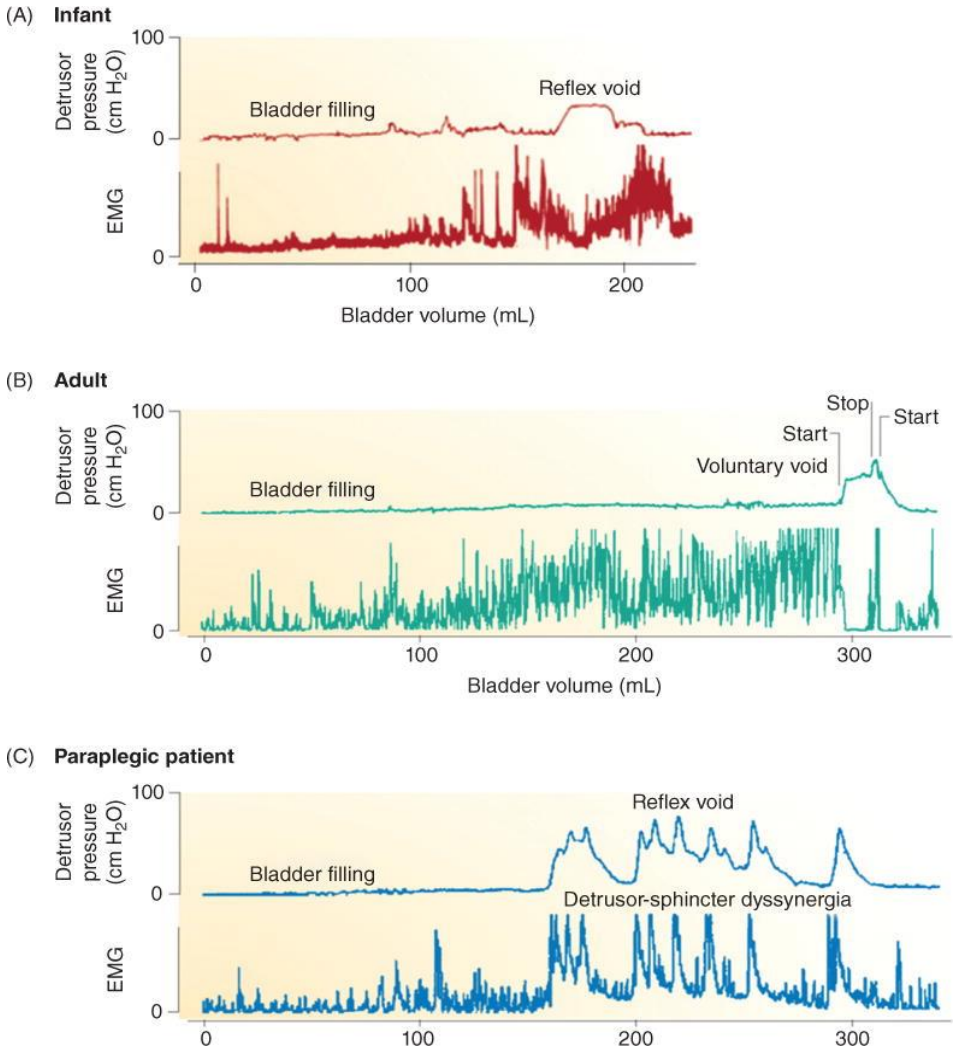

Figure (3): Voiding reflexes in infants, adults and paraplegic patients, based on neural control of micturition by Fowler et al., 2008. Voiding cystometrograms with sphincter electromyograms in an infant (**a**) and in a paraplegic patient (**c**) with a voluntary voiding response in a healthy adult (**b**). In Fig **b** the start of sphincter relaxation, which precedes the bladder contraction by a few seconds, is indicated ('start'). Note that a voluntary cessation of voiding ('stop') is associated with an initial increase in sphincter EMG. In the infant (**a**) sphincter relaxation is present but less complete. On the other hand, in the paraplegic patient (**c**) the reciprocal relationship between bladder and sphincter is abolished.

Cerebral control

Cerebral supervision over micturition reflex maintains voluntary control of voiding. It inhibits micturition except if social circumstances are appropriate and micturition threshold is reached. Multiple areas of the brain take part in this role. Functional MRI studies revealed right inferior frontal area activity during filling of the urinary bladder ***(Griffiths et al., 2005)*** while during voiding there was increased activity in the prefrontal cortex and anterior cingulate gyrus ***(Tadic et al., 2010).***

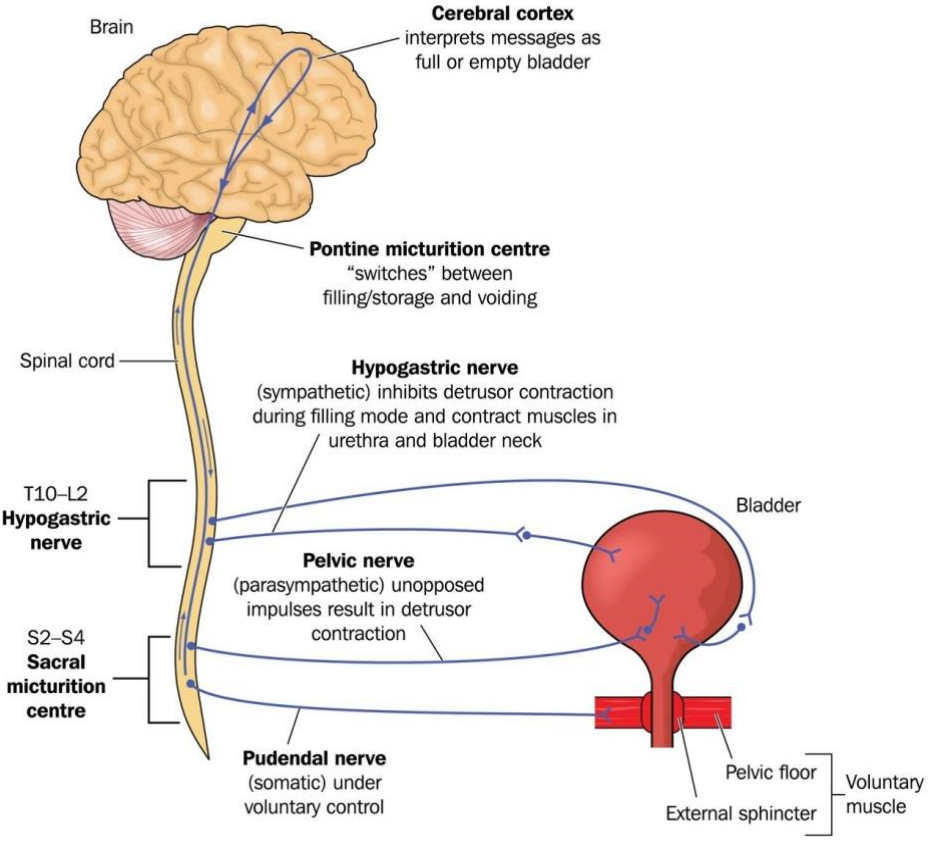

Figure (4): Cerebral control over lower urinary tract, adapted from physical therapy for urinary problems by Saunders, 2013.

Chapter Two

PHARMACOLOGY OF THE LOWER URINARY TRACT

Multiple receptors orchestrate the function of the lower urinary tract. They either act centrally or peripherally as a response to their relevant neurotransmitters. Many drugs affect the lower urinary tract by acting on these receptors with variable efficacy and side effects according to their selectivity and pharmacokinetics ***(Andersson et al., 2004).***

These drugs include Anti muscarinic drugs, Beta adrenergic agonists, and Alpha adrenergic antagonists. It also includes intravesical injection of Onabotulinum toxin A. Other drugs are still under research such as Opioid drugs, GABA agonists and Tachykinins ***(Andersson et al., 2004 and Abrams et al., 2013)***.

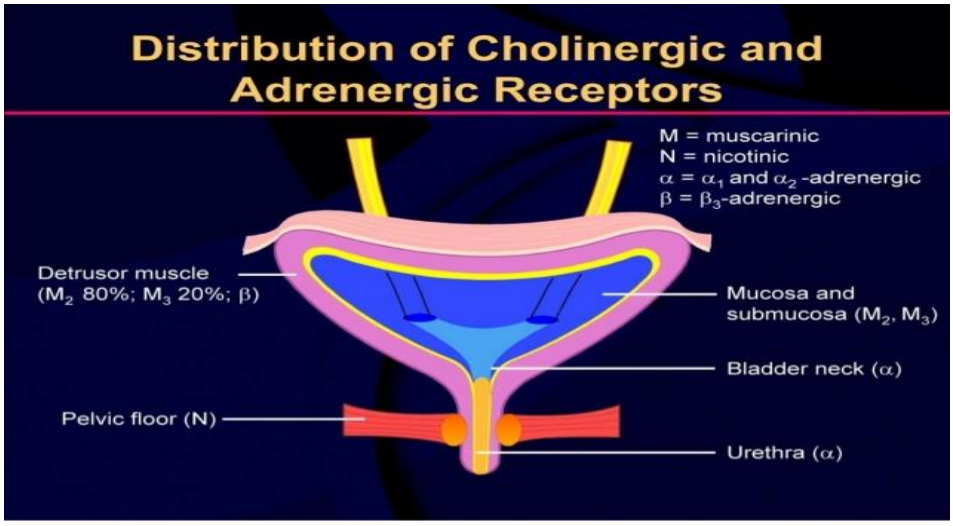

Figure (5): Urinary bladder receptors. Adapted from overactive bladder by Sharda Jain, 2016.