Efficacy of Intradetrusor Injection Of Botulinum Toxin Type A 100 Units Versus 200 Units for the Treatment of Idiopathic Refractory Overactive Bladder

Thesis
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Introduction

Overactive bladder (OAB) symptoms (urgency, frequency, nocturia and urge incontinence) are frequent complaints of patients attending urology and gynecology clinics. In many patients, the cause for these symptoms is detrusor overactivity (DO) which in most cases is idiopathic with no obvious underlying neurological abnormality. Patients with DO also suffer from sleep disturbance, psychological distress and disruption of social and work life. Quality of life scores are consistently reduced in this group of patients (Govier et al, 2001).

There are a variety of treatment options available for the treatment of OAB. The simplest involve advice on fluid intake. Encouraging an adequate but not excessive fluid intake (1.5 L per day). Bladder retraining is often beneficial in short term but many patients relapse. Supervised pelvic floor muscle training can reduce particularly urgency in some patients (Chapple et al,2008).

The mainstay of treatment currently is the use of anticholinergic drugs. Although there has been considerable development in these drugs over the last decade, with more bladder specific preparations available, many patients even if they find them effective can struggle with side-effects. These commonly include dry mouth, constipation and heartburn. Of particular concern in the elderly, is possible cognitive side-effects seen with some drugs such as confusion or memory loss which may limit their use. New approaches such as using a transdermal route of administration may be helpful in reducing the side-effects although skin irritation can be a problem (Brazelli et al, 2006).
Newer second line treatment options include the use of intravesical botulinum toxin, sacral nerve stimulation and percutaneous posterior tibial nerve stimulation. (Casanova et al, 2006).

Intradetrusor injection of botulinum neurotoxin type A (BoNTA) is emerging as the second-line treatment for refractory OAB symptoms. (Apostolidis et al 2009)

Botulinum toxin is a purified neurotoxin derived from clostridium botulinum. The main effect of botulinum toxin is to inhibit signal transmission at the neuromuscular junction by inhibiting the release of acetylcholine. In addition, botulinum toxin is now thought to have effects on the release of other sensory neurotransmitters; such as substance P and ATP, as well as reducing the axonal expression of capsaicin and purinergic receptors. (Chuang et al 2010)

Many studies demonstrated significant improvements in OAB symptoms and QoL, but they also showed increased post void residual urine, acute urinary retention and urinary tract infections. (Denys et al 2012)

There is no consensus on the dose of BoNTA or BoNTB, injection sites, and the duration between repeat injections. (Kuo, 2009)

This study aimed to evaluate the efficacy and safety of a single intradetrusor injection of BoNTA alone comparing two different doses (100 U or 200 U) in patients with IOAB.
Aim of the work

The aim of this study is to assess the efficacy of intradetrusor injection of botulinum toxin type A 100 u versus 200 u for the treatment of idiopathic refractory overactive bladder.
Anatomy of the urinary bladder

The urinary bladder is a hollow viscus with a strong muscular wall. It is characterized by its distensibility. It is a temporary reservoir and varies in size, shape, position and relations according to its content and the state of neighboring viscera. When empty, it lies entirely in the lesser pelvis but as it distends it expands antrosuperiorly into the abdominal cavity in some individuals, a full bladder may ascend to the level of umbilicus (Glass, 2005).

The bladder is located anterior to the vagina, uterus, and cervix in the female (figure 1), while in the male it is superior to the prostate and antroposterior to the seminal vesicles (figure 2). Antroinferiorly; the bladder is supported by the symphysis pubis. The space between the anterior bladder wall and the posterior aspect of the symphysis pubis is known as anterior perivesical space or space of Retzius (Moore et al, 2010).

Figure 1: median sagital section through female pelvis showing the urinary bladder relations. Quoted from (Glass,2005).
The bladder is made of smooth muscle (Detrusor muscle). It is adapted for mass contraction, not peristalsis. The muscle is lined by mucus membrane, surfaced by transitional epithelium. It has an approximate shape of a three-sized pyramid. There are two inferolateral surfaces cradled by anterior parts of levatorani, a neck where the urethra opens, and a superior surface, which is the one that most obviously moves when the bladder fills (Brooks, 2007).

When empty, the bladder is somewhat tetrahedral, and is described as having a superior surface with an apex at the urachus, two inferolateral surfaces which slopes downwards and medially to meet its fellow, lying against the front part of the pelvic diaphragm and obturator internus, and a base (fundus) of the bladder is the posterinferior surface (Glass, 2005), with the bladder neck at the lowest point where the urethra opens (Brooks, 2007).
The apex: superoanterior portion of the bladder and it is relatively thin portion and is quit distensible. The vesical apex in both sexes faces towards the upper part of the symphysis pubis. The urachus anchors the bladder apex to the anterior abdominal wall. The urachus is composed of longitudinal smooth muscle bundles derived from the bladder wall. Near the umbilicus, it becomes more fibrous and usually fuses with the obliterated umbilical arteries. There are no hard and fast dividing lines between the various surfaces especially when distended (Brooks, 2007).

The base (fundus) of the bladder is the posteroinferior surface and it is triangular in shape. In females it is closely related to the anterior vaginal wall; in males it is related to the rectum although it is separated from it above by the rectovesical pouch and below by seminal vesicle and vas deferens on each side (Moore et al., 2010).

The trigone (figure 3) is a triangular area at the base of the bladder lying between the two ureteral orifices (above and laterally) and the internal urethral orifice (centrally and below). In the empty bladder, these three openings are 2.5 cm apart from each other but when distended, the uretral orifices may be 5 cm apart (Tanagho and McAninch, 2008).
Figure 3: Interior of the urinary bladder showing the trigone and its relations.

Quoted from (Glass, 2005).

In the triangular area between the vasa deferentia, the bladder and rectum are separated only by the rectovesical fascia, commonly known as Denonvillier’s fascia. The inferior part of this area may be obliterated by approximation of the ampullae of the vas deferens above the prostate (Glass, 2005).

The muscle of the trigone forms three distinct layers: 1- a superficial layer derived from the longitudinal muscle of the ureter, 2- a deep layer, and 3- a detrusor layer. The urothelium overlying the muscular trigone is usually only three cells thick and adherent strongly to the underlying muscle by a dense lamina propria. During filling and emptying of the bladder, this mucosal surface remains smooth. (Brooks, 2007).
The neck is the lowest region and is also the most fixed. It is 3-4cm behind the lower part of the symphysis pubis, which is a little above the plane of the inferior aperture of the lesser pelvis. Toward the neck of the male bladder, the muscle fibers form the involuntary internal urethral sphincter. This sphincter contracts during ejaculation to prevent retrograde ejaculation (figure 4) (Moore et al, 2010).

Figure 4: bladder neck and sphincter of the urinary bladder

Quoted from (Moore et al, 2010).

This sphincter is not a true circular sphincter but a thickening formed by interlaced and covering muscle fibers of the detrusor as they pass distally to become the smooth muscle of the urethra (Tanagho and McAninch, 2008).

In males the neck rests on, and in direct continuity with the base of the prostate; in females it is related to the pelvic fascia, which surrounds the upper urethra (Tanagho, 2008).
In males the superior surface of the urinary bladder is covered by *peritoneum* (*figure 5*). Anteriorly, the peritoneum sweeps gently on to the anterior abdominal wall with distention; the bladder rises out of the true pelvis and separates the peritoneum from the anterior abdominal wall. Posteriorly, the peritoneum, passes to the level of the seminal vesicles and meets the peritoneum on the anterior rectum to form the rectovesical space (*Brooks, 2007*).

![Figure 5: Relations of peritoneum to the bladder and rectum. The arrow points to the rectovesicalpouch. Quoted from (Glass, 2005).](image)

In the female (*figure 6*), the peritoneum on the superior surface of the bladder is reflected over the uterus to form the vesicouterine pouch and then extends posteriorly over the uterus as rectouterine pouch.

In infants, the true pelvis is shallow and the bladder neck is level with the upper border of the symphysis. The bladder is a true intra-abdominal organ that can project above the umbilicus when full. By puberty, the bladder has migrated to the confines of the deepened true pelvis. (*Brooks, 2007*)
Figure 6: The peritoneum covering the female urinary bladder.

*Quoted from (Moore et al, 2010).*
**Endoscopic Anatomy of Urinary Bladder**

The mucosa is formed of transitional epithelial cells that flatten and form a single epithelial layer during bladder distension. In the distensible portions of the bladder, the mucosa is only loosely attached to the submucosa but is more firmly attached directly to the muscular layer over the trigone. It remains smooth in this area regardless of the state distension since the trigonal area does not distend. In the distensible areas, the mucosal pattern can be related to the degree of filling. The mucosa appears flat when the bladder is filled but can appear redundant or wrinkled when the bladder contains a lesser volume. The normal bladder mucosa is pale, cream red in colour showing small blood vessels radiating and branching underneath (Reuter, 1987).

Fig. 7: conventional cystoscopy reveals normal appearing mucosa.
Points of orientation are the bladder neck with the trigone and ureteric orifices, in one hand, and bladder roof on the other hand (Reuter, 1987).

The bladder neck, which limits the bladder interiorly and distally, appears as a funnel-shaped opening of the urethra into the bladder. Endoscopically, the bladder neck is seen when the instrument passes proximally into the bladder. From that point, the bladder neck appears as a concentric muscular ring. The bladder neck remains the major landmark and reference point in the anatomy of the bladder when viewed from the superior aspect, either with the bladder opened or with an endoscopy placed through a suprapubic tract.

The trigone is formed of two muscle layers superimposed on the detrusor muscle. The superficial trigone is formed as a direct continuation of fibres in the roof and the floor of the intravesical ureter. The deep trigone is formed by direct continuation of Waldeyer's sheath, a fibromuscular structure that completely encircles the distal 3 to 4 cm of the juxtavesical ureter and follows the ureter through the ureteral canal. The sheath (now the deep trigone) continues under the superficial trigone. The trigone and the dense ventral condensation, the middle circular layer of the detrusor, surround the bladder outlet (Tanagho, 2008).
Fig. 8 Lt. ureteric orifice as shown during cystoscopy

The trigone is subjected to many variations with respect to the position of ureteric orifices, its surface area, and angulation. In the male, it frequently extends with several longitudinal urethral folds as far as the verumontanum. Its mucosa is velvety and more strongly colored than that of the remaining bladder; there are no muscular markings of any kind (including spastic or pathologic ones, such as in trabeculation) (Reuter, 1987).

The interureteric ridge is an elevation extending between the ureteral orifices. It is more prominent in males than females, in whom it may, be poorly defined. The ureteral orifices are located along the interureteric ridge symmetrically, usually 1 to 2cm from the midline. There is great variation in the appearance of the normal ureteral orifice. In the adult, a normal, nonrefluxing orifice may have the configuration described as a volcano, a horseshoe, slit-like or some other variation. The orifice may either be quite prominent and obvious
examination or appear as a slit distinguishable from the surrounding mucosa only through careful inspection. The ureteral orifice is often surrounded by a characteristic mucosal vascular pattern. Prominent mucosal vessels course in an arc medial, inferior, and lateral to the orifice. This pattern is often obscured in the presence of generalized mucosal inflammation (Tanagho, 2008).

The base or the fundus of the bladder is located posterior to the trigone. The lateral walls of the bladder extend superiorly to the dome or vertex, as do the anterior and posterior walls. The normal vascular pattern and topographic appearance of the mucosa can be seen over the bladder musculature in these areas (Fig 7). When the bladder is distended, this pattern becomes relatively smooth unless there is prominent trabeculation (Bagley et al., 1985).
Neuroanatomy and neurophysiology of the lower urinary tract

The main function of the lower urinary tract is to store and expel urine. The urinary bladder is a hollow organ with strong muscular wall, the detrusor muscle, which functions as a reservoir. When empty, the bladder is entirely located within the pelvis. As it fills, it can contain about 500 cc or more while it rises into the abdominal cavity. The bladder neck, urethra and pelvic floor form the bladder outlet and facilitate urine evacuation. From both sides the ureters penetrate the bladder in its posterolateral wall after tunneling the bladder wall obliquely over a 1-2 cm long to end as the ureteral orifices. The posterolateral angles formed by the ureters orifices and the internal orifice of the urethra form a triangular area: trigone (Groat, 1993).

The bladder is composed of four layers: serous, muscular, submucosal and mucosal layers. The tunica mucosa is continuous with the lining membrane of the ureters and renal pelvis, and below with that of the proximal urethra. The areolar tissue of the tunica submucosa connects the mucosa only slightly; it makes the bladder look wrinkled when contracted. Over the trigone the mucous membrane is firmly attached to the muscular coat, and thus looks smooth and flat. The tunica muscularis consists of three layers. The internal longitudinal layer is thin; fibers are organized for the most part in a longitudinal direction. In the middle layer, the fibers are irregularly scattered, but circularly arranged toward the lower part forming a thick circular sphincter vesicae around the urethral orifice. The external layer has been named
the detrusor muscle and is composed of fibers organized in a longitudinal arrangement. The outer tunica serosa is derived from the peritoneum (Gray, 1995).

The physiological internal sphincter maintains continence by closure of the bladder neck and proximal urethra. Continence is thought to be dependent on a combination of urethral wall tension, the caliber of the urethral lumen and the functional length. The striated muscles surrounding the urethra are not only essential for urinary continence but are also important in the voluntary termination of urine flow and prevention of stress incontinence (Steers, 1998).

**INNERVATION:**

Storage and expulsion of urine is the result of complex neural network interactions. Different neural circuits located in brain, brain stem, spinal cord and peripheral nerves and ganglia regulate bladder filling and coordinated micturation. Interaction of somatic and autonomic efferent signals, voluntary on-off control mechanism and learned behaviour modulate the lower urinary tract’s function (Boron and Boulpaep, 2003).

**Neural circuits controlling storage and expulsion of urine**

Filling of the bladder and voiding involve a complex pattern of afferent and efferent signaling in parasympathetic (pelvic nerves), sympathetic (hypogastric nerves), and somatic ( pudendal nerves) pathways. These pathways constitute reflexes, which either keep the
bladder in a relaxed state, enabling urine storage at low intravesical pressure, or initiate bladder emptying by relaxing the outflow region and contracting detrusor (Andersson, 2008)

PARASYMPATHETIC PATHWAYS

The sacral parasympathetic pathways mediate contraction of the detrusor smooth muscle and relaxation of the outflow region. The preganglionic parasympathetic neurons are located in the sacral parasympathetic nucleus (SPN) in the spinal cord at the level of S2–S4. The axons pass through the pelvic nerves and synapse with the postganglionic nerves in either the pelvic plexus, in ganglia on the surface of the bladder (vesical ganglia), or within the walls of the bladder and urethra (intramural ganglia). The ganglionic neurotransmission is predominantly mediated by acetylcholine acting on nicotinic receptors, although the transmission can be modulated by adrenergic, muscarinic, purinergic, and peptidergic presynaptic receptors. The postganglionic neurones in the pelvic nerve mediate the excitatory input to the normal human detrusor smooth muscle by releasing acetylcholine acting on muscarinic receptors. However, an atropine-resistant (nonadrenergic, noncholinergic: NANC) contractile component is regularly found in the bladders of most animal species. Such a component can also be demonstrated in functionally and morphologically altered human bladder tissue, but contributes only to a few percent to normal detrusor contraction (O’Reilly, 2002).

Adenosine triphosphate (ATP) is the most important mediator of the NANC contraction, although the involvement of other transmitters cannot be ruled out. (Andersson and Wein, 2004).
Substances acting as neurotransmitters or neuromodulators include an extensive list, e.g., opioids, vasoactive intestinal polypeptide (VIP), serotonin, dopamine, glutamic acid, GABA, ATP, and prostaglandins (F2, E, E2). Many of these substances exhibit both inhibitory and facilitative influence on the micturition cycle at the spinal cord level and higher (Klarskov et al., 1984).

The pelvic nerve also conveys parasympathetic nerves to the outflow region and the urethra. These nerves exert an inhibitory effect on the smooth muscle, by releasing nitric oxide and other transmitters. (Andersson and Wein, 2004).

**SYMPATHETIC PATHWAYS**

The sympathetic innervation of the bladder and urethra originates from the intermediolateral nuclei in the thoracolumbar region (T11–L2) of the spinal cord. The axons leave the spinal cord via the splanchnic nerves and travel either through the inferior mesenteric ganglia (IMF) and the hypogastric nerve, or pass through the paravertebral chain to the lumbosacral sympathetic chain ganglia and enter the pelvic nerve. Thus, sympathetic signals are conveyed in both the hypogastric nerve and the pelvic nerve. The ganglionic sympathetic transmission is, like the parasympathetic preganglionic transmission, predominantly mediated by acetylcholine acting on nicotinic receptors. Some preganglionic terminals synapse with the postganglionic cells in the paravertebral ganglia or in the IMF, while other synapse closer to the pelvic organs, and short postganglionic neurones innervate the target organs. Thus, the hypogastric and pelvic nerves contain both pre- and postganglionic fibre. The predominant effect of the sympathetic innervation is to contract the bladder.
base and the urethra. In addition, the sympathetic innervation inhibits the parasympathetic pathways at spinal and ganglionic levels. In the human bladder, noradrenaline is released in response to electrical stimulation in vitro, and the normal detrusor response to released noradrenaline is relaxation. However, the importance of the sympathetic innervation for relaxation of the human detrusor has never been established. In contrast, in several animal species the adrenergic innervation has been demonstrated to mediate relaxation of the detrusor during filling. (Andersson and Arner, 2004).

The smooth muscle of the bladder and proximal urethra in a variety of animals and in humans contains both α- and β-adrenergic receptors. α-adrenergic contractile responses predominate in the bladder base and proximal urethra, whereas β-adrenergic relaxation responses predominate in the bladder body (Wein and Moy, 2007).

SOMATIC PATHWAYS

The somatic innervation of the urethral rhabdosphincter and of some perineal muscles (eg, compressor urethrae and urethrovaginal sphincter) is provided by the pudendal nerve. These fibers originate from sphincter motor neurons located in the ventral horn of the sacral spinal cord (levels S2–S4) in a region called Onuf’s (Onufrowicz’s) nucleus (Thor and Donatucci, 2004).

AFFERENT PATHWAYS

Afferent axons in the pelvic, hypogastric, and pudendal nerves transmit information from the lower urinary tract to the lumbosacral spinal cord. (Yoshimura and de Groat, 1997).
The primary afferent neurons of the pelvic and pudendal nerves are contained in sacral dorsal root ganglia (DRG), whereas afferent innervation in the hypogastric nerves contained in the rostral lumbar DRG. The central axons of the DRG neurons carry the sensory information from the lower urinary tract to second-order neurons in the spinal cord (de Groat et al, 1996). Visceral afferent fibers of the pelvic and pudendal nerves enter the cord and travel rostrocaudally within Lissauer’s tract (Thor et al, 1989).

The most important afferents for the micturition process are myelinated Aδ-fibers and unmyelinated C-fibers traveling in the pelvic nerve to the sacral spinal cord, conveying information from receptors in the bladder wall. The Aδ-fibers respond to passive distension and active contraction, thus conveying information about bladder filling. The activation threshold for Aδ-fibers is 5–15 mm H2O. This is the intravesical pressure at which humans report the first sensation of bladder filling. C-fibers have a high mechanical threshold and respond primarily to chemical irritation of the bladder urothelium/suburothelium or to cold. Following chemical irritation, the C-fiber afferents exhibit spontaneous firing when the bladder is empty and increased firing during bladder distension. These fibers are normally inactive and are therefore termed “silent fibers.” Afferent information about the amount of urine in the bladder is continuously conveyed to the mesencephalic periaqueductal gray (PAG), and from there to the pontine micturition center (PMC), also called Barrington’s nucleus. (Holstege, 2005; Kuipers et al., 2006).

NORMAL STORAGE

Urine storage involves the bladder’s ability to accommodate increasing volume of urine at a low intravesical pressure. This
relationship is a measure of normal bladder compliance (C) \( C = \frac{\Delta \text{Volume}}{\Delta \text{detrusor Pressure}} \). Effective urine storage requires the bladder outlet to remain closed at rest and during increased intra-abdominal pressure (Wein, 2007).

Afferent signals from the pudendal and pelvic nerves activate the sacral and pontine micturition centers to stimulate increased sphincter tone and decrease parasympathetic detrusor contraction. Sympathetic nerves act to increase urethral resistance during this bladder filling process. Additionally, voluntary squeezing of the sphincter can decrease urinary urgency by activating the inhibitory reflex arc (Tanagho, 2008).

**NORMAL VOIDING**

Coordinated voiding similarly involves the sacral and pontine micturition centers. The micturition reflex coordinates the interaction between the detrusor muscle and urethral sphincter. The activation of the micturition reflex occurs in response to the stimulation of tension receptors and nociceptors in the bladder wall caused by bladder distension (Wein, 2007).

Bladder afferent nerve impulses travel to the sacral cord triggering detrusor contraction, bladder neck and sphincter relaxation. The cycle of micturition is then initiated by the relaxation of the striated urethral sphincter and the pelvic floor muscles. This results in a decrease in the urethral pressure. The bladder then contracts, and this increase in detrusor pressure results in urine flow as the intravesical pressure equals and then exceeds the intraurethral pressure (Blaivas, 1985).

Normally, the brain stem modulates the reflex such that the bladder contraction is appropriately sustained to allow for complete emptying. Following voiding, the detrusor muscle receives efferent
inhibitory signals and the intraurethral pressure increases as the striated urethral sphincter contracts to again allow for storage of urine (Blaivas, 1985).

Figure 9
Storage and voiding reflexes of the bladder. (Hassouna et al., 2008)
**The Overactive bladder**

**Definition:**
Overactive bladder (OAB) is defined as a symptom complex comprising urinary urgency, with or without urgency incontinence, usually with frequency and nocturia in the absence of pathological or metabolic disorders (Abrams et al., 2002).

Urgency is the hallmark of OAB, and is defined as the sudden compelling desire to urinate which is difficult to defer. OAB is a clinical diagnosis, distinct from the diagnosis made on urodynamic assessment of detrusor overactivity (DO). The overlap between urodynamically-defined DO and subjectively-reported OAB is substantial, but many people with OAB do not have DO and people with DO do not always have urgency (Hashim and Abrams, 2006).

**Prevalence:**

The prevalence of OAB increases with age. From the epidemiological studies conducted to date, it can be concluded that of those patients with OAB, approximately one-third are troubled by incontinence (OAB ‘wet’) and two-thirds are not (OAB ‘dry’). The NOBLE (National Overactive Bladder Evaluation) study estimated the overall prevalence of this condition in the US population to be 16% in men and 16.9% in women. As the population ages, an overall increase in prevalence occurs (Stewart et al., 2003).

A Japanese epidemiological survey estimated a slightly lower overall incidence (12.4%) in the general population aged over 40, but the prevalence increased with age, with more than 20% of people older than 70 years and more than 35% older than 80 suffering lower urinary tract symptoms (Homma et al., 2003).
More available data from the EPIC (European Prospective Investigation into Cancer and Nutrition) Study suggest that the prevalence of OAB symptoms (using the 2002 International Continence Society (ICS) definition) is closer to 12% in the community; and of these sufferers, approximately 50% experience significant bother from their symptoms (Irwin et al., 2006).

Abdelwahab and his colleagues in 2011 in their study on Outcomes of the urogenital distress inventory (UDI-6) for 20- to 50-year-old females with lower urinary tract dysfunction in Qalubia Governorate, Egypt, urge incontinence was present in 22.2% of patients, The presence of mild and moderate stress incontinence and mild urge incontinence increased significantly in patients who were 41-50 years old. Micturition difficulty and micturition frequency occurred in < 7% of patients (Abdelwahab et al., 2011).

Pathophysiology:

The exact cause of idiopathic OAB is not well defined. Several theories regarding the etiology of OAB have been proposed:

- **Neurogenic Theory:**

  The neurogenic theory states that detrusor overactivity arises from generalized, nerve-mediated excitation of the detrusor muscle. There are several interdependent mechanisms by which this may arise. **First**, damage to the brain can induce detrusor overactivity by reducing suprapontine inhibition. **Second**, damage to axonal pathways in the spinal cord allows the expression of primitive spinal bladder reflexes. **Third**, synaptic plasticity leads to reorganization of sacral activity, with the emergence of new reflexes, which may be triggered by C-fiber bladder
afferent neurons. Finally, sensitization of peripheral afferent terminals in the bladder can trigger detrusor overactivity (de Groat, 1997).

- **Increased myogenic activity of detrusor smooth muscles:**

  This is an important mechanism inducing OAB and detrusor overactivity, which seems to be more applicable to patients with bladder outlet obstruction (BOO). Partial BOO increases intravesical pressure and induces bladder hypertrophy and partial denervation of the bladder smooth muscle, leading to various functional changes in smooth muscles. These changes include denervation supersensitivity of cholinergic (muscarinic) receptors, increases in purinergic receptor–mediated contractile responses as well as expression of purinergic receptors such as P2X1 (Boselli et al., 2001), and changes in the cell-to-cell communication in detrusor muscles due to up-regulation of gap-junction proteins such as connexin. Thus, increases in receptor-mediated muscle contractility and interaction between smooth muscles cells can result in coordinated myogenic contraction of the entire bladder and detrusor overactivity (Haferkamp et al., 2004).

  It has been suggested that local contraction (activity) that occurs somewhere in the detrusor will spread throughout the bladder wall, resulting in coordinated myogenic contraction of the whole bladder. This local contraction in the bladder wall has been shown to generate afferent discharge (Drake et al., 2005).

  Localized bladder activity was assessed by the micro-motion detection method, demonstrating that women with increased bladder sensation on filling cystometry had a significantly higher prevalence of localized activity than the control group. This observation suggests that localized distortion of the bladder wall simulates afferent activity which
would precipitate a feeling of urgency and detrusor overactivity (Drake et al., 2005).

In addition, another population of cells in the bladder known as interstitial cells has been proposed for a pace-making role in spontaneous activity of the bladder. Because it has been reported that the number of interstitial cells is increased in a guinea-pig model of BOO (Kubota et al., 2007) and that c-kit tyrosine kinase inhibitors, which inhibit interstitial cell activity, decreased the amplitude of spontaneous contractions in the guinea-pig and human bladder, interstitial cells may also be involved in the emergence of detrusor overactivity because of enhanced autonomous detrusor muscle activity (Biers et al., 2006).

- **Role of non-neuronal Ach and the muscarinic receptors:**

  Recently, new evidence suggests an increased release of acetylcholine (Ach) during urine storage, both from neuronal and non-neuronal (including urothelium) sources. The release can be enhanced by distension of the bladder and increases with advancing age, and it appears to contribute to the pathophysiology of OAB (Andersson, 2011).

  Ach is the main contractile transmitter in the human bladder. It is released from postganglionic efferent cholinergic (parasympathetic) nerves, acts on muscarinic receptors, and produces the contraction that empties the bladder (Giglio, 2009).

  However, there is also a non-neuronal release of ACh that may be involved in other bladder functions. Recent studies analyzed the content of ACh in the urothelium and characterized the molecular components of its synthesis and release machinery. They found ACh to be present in the urothelium in a nanomolar range per gram of wet weight. This means that the urothelium is a source of ACh, it also implies that muscarinic
receptors within the urothelium and underlying structures can be targets for antimuscarinic drugs (Lips, 2007).

It may be assumed that during the storage phase, there is an ongoing release of ACh from nerves or from a non-neurogenic source, possibly the urothelium. ACh may then act indirectly, by release of other mediators, or directly on afferent nerves to initiate the micturition reflex or enhance the myogenic (spontaneous) contractile activity of the detrusor. This activity seems to be increased in patients with DO, in turn increasing “afferent noise” (Andersson, 2010).

There is normally no parasympathetic outflow from the spinal cord during filling. Nevertheless, the bladder maintains a “tone” and exhibits non synchronized local contractions and relaxations, and this is believed to be caused by a myogenic contractile activity that is reinforced by release of mediators from non-neuronal (urothelium, lamina propria, other structures) as well as neuronal sources. There are reasons to believe that the spontaneous contractile phasic activity of the detrusor smooth muscle during filling can generate afferent input “afferent noise” and that in pathologic conditions (e.g., OAB), this input may contribute to these disorders (Gillespie, 2009).

Finally, there may be a combined etiology secondary to an abnormal leak of acetylcholine that cause micro-motions in the bladder smooth muscle, which in turn stimulates the CNS, leading to the sensation of urgency (Andersson, 2004).

Symptomatology:

Symptoms of bladder overactivity as defined by ICS (Abrams et al, 2002):
• **Increased day time frequency:** is the complaint of voiding too often by day.

• **Nocturia:** is the complaint that the individual has to wake at night one or more times to void.

• **Urgency:** is the complaint of sudden compelling desire to pass urine which is difficult to defer.

• **Urge incontinence:** is the complaint of involuntary leakage of urine accompanied by or immediately preceded by urgency.

**Risk Factors:**

Risk factors most commonly associated with OAB and incontinence include age 75 years and older, arthritis, chronic lung disease, depression, diminished cognitive status and delirium, fecal impaction, hysterectomy, immobility, increased BMI in women, diabetes, lumbar disk disease, multiple vaginal deliveries, stroke, urinary tract infection, vaginal or bladder surgery, and white race. Individuals taking alpha-adrenergic blockers, alpha-adrenergic agonists, anticholinergics, antimuscarinics, antidepressants, antipsychotics, beta-adrenergic agonists, calcium channel blockers, diuretics, hormone replacement therapy, hypnotics, and/or sedatives are also at increased risk of developing OAB symptoms (**Rosenberg and Dmochowski, 2005**).

**Co morbidities:**

OAB has a negative effect on quality of life. Patients limit their fluid intake, avoid sexual intimacy, wear pads and map the location of toilets also depression, sleep deprivation, urinary tract infections, skin infections, and orthopedic injuries resulting from falls related to OAB (**Rosenberg and Dmochowski, 2005**).
Diagnosis and Evaluation:

Initial evaluation of lower urinary tract symptoms suggestive of OAB typically includes a history, physical examination, urine analysis, and bladder diary evaluation is designed to rule out medical and non-medical etiologies for lower urinary tract symptoms, such as functional impairments, medication side effects, urinary tract infections, bladder outlet obstruction, bladder tumors, or neurologic etiologies, such as stroke or multiple sclerosis. In most individuals, a diagnosis of OAB can be made based on these components, and treatment can be started (Starkman and Dmochowski, 2008).

Symptomatic diagnosis of OAB does not correlate with a urodynamic diagnosis of detrusor instability. The diagnosis of overactive bladder based on urinary symptoms underdiagnoses the condition of detrusor instability in a population of women suffering from lower urinary tract symptoms. Therefore, symptomatic diagnosis of OAB alone is not recommended (Digesu et al., 2003).

Urodynamic testing is not required for an initial diagnosis of OAB. An increasing body of evidence suggests that, although there is a relationship between the urodynamic finding of detrusor overactivity and OAB, these are quite separate findings, and successful response to nonsurgical and surgical interventions for OAB does not depend on finding detrusor overactivity on urodynamic testing. The role of urodynamics in the setting of OAB is not well defined at present, but there are several clinical scenarios where such testing may be useful. However, at this time, the evidence to support their routine use in patients with OAB is limited (Rovner and Goudelocke, 2010).
Urodynamic evaluation should be done only if it is going to change patient treatment or help differentiate the etiology of voiding dysfunction, or if it is done after failed conservative/medical treatment (Colli et al, 2003).

Figure 10

a) Urodynamic chart in a case of OAB with detrusor overactivity.

b) Urodynamic chart in a case of OAB without detrusor overactivity (Colli et al, 2003)

**Differential diagnosis:**

Distinguishing OAB from common cause of urgency should be made. Urine analysis can easily exclude urinary tract infection as a common cause of lower urinary tract symptoms. Blood glucose level can exclude frequency due to diabetes mellitus. Old age patients suspicious of having malignancy are candidates for pelvi-abdominal ultrasonography.
which can also exclude—in combination with digital rectal examination—the presence of prostatomegaly in male patients.

The major disorder to be differentiated from OAB is painful bladder syndrome which is defined as the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased day-time and night-time frequency, in the absence of proven urinary infection or other obvious pathology therefore, as the key symptom of OAB urgency is defined as the complaint of a sudden compelling desire to pass urine, which is difficult to defer (for fear of leakage), then the key symptom of PBS is bladder pain. (Abrams et al., 2005).

When discussing symptoms with patients it can help to discuss the differences in sensation between the two conditions. In PBS, sensation builds to discomfort and then to pain and is felt suprapubically even if the patient also has perineal (urethral/vaginal/penile) discomfort/pain. In OAB, urgency is usually described as being felt lower down than the sensations of bladder filling and the normal desire to void. In men it is felt in the perineum/base of penis and in women in the vagina/urethra. (Abrams et al, 2005).

In OAB, urgency incontinence occurs in 50% of patients. In PBS, incontinence is uncommon although a small number of patients experiencing severe pain will voluntarily pass (‘‘leak’’) urine onto a pad or even into their underwear because they know that the reduction of bladder capacity, by even 10ml, will significantly reduce their pain: this is not urgency incontinence. Similarly, their pain does not give urgency (for fear of leakage) and it is perhaps better to say that they have a ‘‘desperate desire to void because of pain and fear of worsening pain’’. (Abrams et al., 2005).
In PBS, voided volumes are habitually small; both by day and by night, and a frequency volume chart should be completed to document the extent of the patient’s symptoms and the degree to which voided volumes are reduced. Most PBS patients will have a consistent voided volume below 250 ml. Occasional PBS patients have little frequency because they severely restrict their fluid intake and may sometimes avoid suffering nocturia by this maneuver (Abrams et al., 2005).
Quality-of-Life Issues in Incontinence

1-Impact of urinary incontinence on health related quality of life

Although urinary incontinence is traditionally thought of as a condition that affects quality of life, there are few studies that quantify the impact of this health problem on general health related quality of life. However, the studies that have been performed clearly demonstrate that this condition has a broad effect on quality of life. Using the Nottingham Health Profile, Grimby and his colleagues (Grimby, et al 1993) measured general HRQOL in 120 elderly women (mean age 75.4 years) with urinary incontinence. As a comparison group, 313 age-matched women without urinary incontinence also completed the questionnaire. They found that incontinent women experienced greater emotional disturbance and social isolation than the age-matched controls.

In another study, Haggland et al (Hagglund, et al 2001) used a population-based approach to assess the impact of stress and urge incontinence on HRQOL in Surahammar, Sweden. HRQOL data were available in 596 women without incontinence, 440 women with stress incontinence, and 71 women with urge incontinence. Incontinent women, regardless of type, reported significantly lower general HRQOL scores in all eight domains of the SF-36. However, when stratified by type of incontinence, women with urge incontinence reported significantly worse general HRQOL in all domains even when compared to women with...
stress incontinence. The magnitude of difference in general HRQOL scores between women with stress, as opposed to urge, incontinence was particularly striking, 10–20 points lower in all domains, and underscore the clinical importance of these findings. Similarly, Hunskaar and Visnes used the Sickness Impact Profile to specifically compare women with urge incontinence to those with stress incontinence and found that the group with urge incontinence had significantly worse HRQOL in the sleep and social interaction domains of the SIP. In addition, they divided their cohort by age, comparing HRQOL in 36 incontinent women aged 40–60 years and 40 women age 70 years, while controlling for type of incontinence. Younger women had worse HRQOL than older women, particularly in the domains of emotional behavior and effect on recreation and pastimes. This study demonstrates that the effect of incontinence on general HRQOL is affected not only by the type of incontinence but also by the age of the patient. Interestingly, it is not simply incontinent episodes that affect quality of life in urge incontinence.

In a telephone study of overactive bladder (OAB), (O’Conor, et al 1998) Liberman and colleagues administered the SF-36 to 483 subjects with OAB symptoms and 191 controls. After adjusting for age, sex, and use of medical care, subjects with incontinent OAB (n = 185) had worse HRQOL in the physical function, role-functional, bodily pain, health perceptions, social functioning, and mental health domains of the SF-36 when compared to controls. However, in the subgroup of patients with overactive bladder symptoms and no incontinence (n = 298), significantly lower HRQOL scores were still noted in the role-functioning, mental health, health perception, and bodily pain domains. The investigators further divided this population into continent OAB patients with frequency only (n = 175), urgency only (n = 80), and both
frequency and urgency symptoms (n ¼ 43). Of these three subgroups, only patients with continent OAB who experience both frequency and urgency have significant lower HRQOL scores than controls. This association was noted in all domains except for social function. This study and others (O’Conor ,et al 1998) indicate that, while much of the quality of life impact of urge incontinence is due to the actual leakage episodes, the combination of frequency and urgency symptoms, in and of itself, also affects quality of life (Nirit ,et al 2005).

Furthermore, in the 230 subjects who reported urinary incontinence, lower domain scores in physical and mental health, life satisfaction, and the perception that incontinence interfered with daily life were significant predictors of depression .(Dugan ,et al 2000)

Other studies have found a similar relationship between urinary incontinence and depression and social isolation (Melville, et al 2002, Fultz, et al 2001).

In conclusion, urinary incontinence and lower urinary-tract symptoms appear to impact health related quality of life extensively, affecting physical, psychological, and emotional domains to a greater degree than clinicians might expect (Nirit, et al 2005).

2-Impact of incontinence treatment on health related quality of life

Given the broad impact of urinary incontinence on health-related quality of life as described above, it is important that we document that treatment for urinary incontinence result in improved quality of life for our patients. Although the field of health-related quality-of-life research in urinary incontinence is still young, several authors have used validated

**QoL Assessment**

There is many validated questionnaires used for evaluating QOL effect on patients with OAB as: EQ-5D and SF-36.

**EQ-5D**: The EQ-5D consists of two parts: the health states descriptive system and the visual analog rating scale (VAS). The descriptive system records the level of self-reported problems on each of the five dimensions of the classification (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). For each dimension the respondent is asked to choose between three options: no problem, some/moderate problems, or extreme problems/unable. Health states defined by the five-dimensional descriptive system can be converted into a weighted health state index by applying scores from value sets elicited from general population samples (Kind, 2003).

Respondents then describe their own health status using a VAS. A 20-cm vertical VAS has become the standard means of obtaining valuations for health states. The endpoints of the VAS are labeled “best imaginable health state” and “worst imaginable health state” anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health state by drawing a line from an anchor box to that point on the VAS that best represents their own health on that day (Brooks, 1996).

UK English, Spanish, and German versions have been adapted culturally and translated (Rabin and de Charro, 2001).
SF-36: The Medical Outcomes Trust Short Form 36- Item Health Survey (SF-36) is a generic measure of functional status and well-being. (Ware, et al 1993).

It contains 36 questions that measure health across eight dimensions—physical functioning (PF), role limitations because of physical health (RP), role limitation because of emotional health (RE), social functioning (SF), bodily pain (BP), mental health (MH), vitality or energy (VT), and general health perception (GH). Responses to each question within a dimension are combined to generate a score from 0 to 100, where 100 indicate “good health” and 0 indicates “poor health.” (Ware, et al 1993).
Management of Overactive Bladder

The International Consultation on Incontinence (ICI) algorithms divides management into initial treatment and specialized therapy (Abrams et al., 2010).

A combination of both behavioral and pharmacological therapy is considered to be the standard of care for the initial control of OAB symptoms; however, treatment strategies should be tailored according to the patient’s needs and expectations, and management goals should be shared with patients with an emphasis on controlling the symptoms and not curing the underlying condition. (Abrams et al., 2010).

The treatment mainly aims to reduce the sensation of urgency, increase the voided volume, reduce frequency, and eliminate leakage episodes. If OAB symptoms fail to be controlled by these measures, sacral nerve stimulation (SNS) or any other form of neuromodulation can be introduced to alleviate patient symptoms. If sacral neuromodulation proves to be ineffective, surgery is the last option that can be offered to these patients. (Abrams et al., 2010).

**Behavioral therapy:**

Components of behavioral therapy include education, timed voiding, delayed voiding, dietary modifications, and pelvic floor muscle exercises.

Behavioral therapy starts with education. Patients need to be educated regarding normal bladder function and normal voiding habits. Timed voiding involves voiding at set intervals, regardless of the urge to void, which may help to decrease the risk of urinary urge incontinence (UI) and urgency (Wyman, 2009).
In some individuals, caffeinated, spicy, and acidic foods and drinks may exacerbate symptoms, and thus, dietary restrictions may lead to improvement in symptoms. Normalizing fluid intake may also prove helpful; too much or even too little fluid may exacerbate symptoms because concentrated urine may act as a bladder irritant (Dallosso et al., 2004).

Individuals suffering from urgency and frequency, but not incontinence, may benefit from urgency suppression techniques and delayed voiding, which involves trying to hold urine for progressively longer periods of time by consciously suppressing the urge to void, as well as tightening pelvic floor muscles. Pelvic floor muscle exercises may also help decrease urgency and incontinence when properly performed. A bladder diary is useful in behavioral therapy because it allows patients to track their responses and identify possible factors that exacerbate their symptoms (Miller and Sand, 2007).

**Pharmacotherapy:**

**Antimuscarinics:***

There are a number of pharmacological mechanisms that could reduce overactivity of the detrusor muscle. However, antimuscarinic drugs are approved treatment as Grade A recommendation (Andersson et al., 2009).

Antimuscarinics are the primary medical treatment for OAB of all ages. They exert their biological effects by competitively binding to the muscarinic receptors on the detrusor muscle (M2 and M3 subtypes), thereby preventing acetylcholine’s positive effects on contractility. They have been shown to reduce micturition frequency, urge incontinence episodes, and nocturia (Chapple et al., 2008).
Oxybutynin, Tolterodine, propiverine, solifenacin, darifenacin, trospium and fesoterodine are antimuscarinic agents approved for use in OAB treatment.

**Oxybutynin:**

Oxybutynin is the first antimuscarinic used for the treatment of OAB. In addition to its antimuscarinic action, Oxybutynin in high doses exerts muscle relaxant and local anesthetic effects (Siddiqui et al., 2004).

Oxybutynin is now available in oral, immediate (IR) and extended-release (ER), as well as two transdermal formulations, a patch and a gel. An intravesical formulation of Oxybutynin has also been studied (Hanawa et al., 2008).

Oxybutynin IR formulation was the first that entered clinical practice. Despite its satisfactory efficacy, the substantial incidence of dry-mouth, immediate release oxybutynin’s most common and bothersome side-effect, limited its tolerability. Newer formulations aimed at eliminating peaks in concentration of Oxybutynin and its metabolites in order to reduce related side-effects (Siddiqui et al., 2004).

The ER formulation of Oxybutynin provides a smooth plasma concentration profile over the 24-hour dosage interval, facilitating once-daily administration. Hence, given its overall efficacy/tolerability and dose flexibility, Oxybutynin ER provides an alternative in the first-line of pharmacotherapy for OAB (Siddiqui et al., 2004).

Overall, as shown in the OPERA (Overactive bladder: Performance of Extended Release Agents) study, Oxybutynin ER has modestly greater efficacy than tolterodine IR at its most commonly prescribed dose (Diokno et al., 2003).
In the OBJECT (Overactive Bladder Judging Effective Control and Treatment) study oxybutynin ER was more effective than tolterodine at the endpoints of urge incontinence, total incontinence, and micturition frequency episodes (Appell et al., 2001).

The transdermal oxybutynin (OXY-TDS) formulation offers patients with urinary incontinence an effective, safe and well-tolerated option for managing the symptoms of overactive bladder (Sand et al., 2007). As OAB contributes to decreased work productivity due to job interruptions as well as fatigue, the use of transdermal oxybutynin may result in productivity improvement when patients receive 3.9 mg/day via twice weekly patch application for up to 6 months (Pizzi et al., 2009).

Oxybutynin chloride topical gel (OTG) was approved in January 2009 by the US FDA. OTG was designed to provide steady plasma oxybutynin levels with daily application, favorably altering the circulating N-desethyloxybutynin metabolite to oxybutynin ratio, thus minimizing the antimuscarinic adverse effects of oral formulations. The use of a biocompatible delivery system also reduced the application-site skin reactions associated with other available forms of transdermal delivery. OTG represents an efficacious, safe, and convenient alternative to other oxybutynin formulations and oral antimuscarinics for the treatment of OAB (Staskin et al., 2009).

Interestingly, all the above mentioned oxybutynin formulations have been shown to be more efficacious than the IR oxybutynin in respective trials (Novara et al., 2008).

- **Tolterodine:**

  Tolterodine is a widely prescribed antimuscarinic and it was the first specifically developed to treat OAB. Tolterodine is not selective for
any muscarinic receptor subtype but it exhibits selectivity for the urinary bladder over salivary glands in vivo (Nilvebrant et al., 1997).

An IR formulation was available first, but an ER, administered once-daily, formulation was later designed. Its efficacy and tolerability have been proved in a large number of trials. Tolterodine offers significant improvement in overactive bladder symptoms and quality of life while having a favorable safety profile. It soon became the gold-standard in the class, a drug that all others are compared to, during their clinical development (Salvatore et al., 2008).

Oxybutynin and tolterodine, most commonly prescribed antimuscarinics, have been shown to have similar efficacies in general OAB populations, as well as in specific subpopulations defined by severity of urodynamic findings (Giannitsas et al., 2004).

• **Propiverine:**

Propiverine, another muscarinic receptor antagonist, has also been demonstrated to inhibit L-type Ca++ channels in high concentrations (Madersbacher and Murtz, 2001).

Propiverine has similar efficacy to oxybutynin and tolterodine, similar tolerability and impact on quality of life to tolterodine, but a better tolerability profile than oxybutynin. This drug is well tolerated (Junemann et al., 2005).

Propiverine and oxybutynin are efficacious in children with incontinence due to overactive bladder and propiverine is officially approved in certain countries for pediatric use. Alloussi et al. evaluated existing evidence for the use of antimuscarinics in children. They
concluded that high-quality studies are still limited and results vary widely across antimuscarinics. (Alloussi et al., 2010).

The daily urgency episodes were significantly reduced from baseline to 12 weeks on propiverine treatment, compared with placebo. Secondary endpoints, including sum of urgency severity per 24 h, urgency severity period, and daytime voiding frequency, were also improved significantly in the propiverine group (Lee et al., 2010).

- **Darifenacin**

  Darifenacin is the antimuscarinic with the highest M3 receptor subtype selectivity. Long-term darifenacin treatment was associated with significant and clinically meaningful improvements in quality of life of patients with urge incontinence (“wet” OAB) over 2 years (Dwyer et al., 2008).

  In a study of patients who were dissatisfied with their previous treatment with oxybutynin ER or tolterodine ER, Patients OAB symptoms were significantly improved, and satisfaction was high during treatment with darifenacin 7.5 or 15 mg (Zinner et al., 2008).

- **Solifenacin**:

  A pooled analysis of four randomized, placebo-controlled, phase III studies of solifenacin in OAB patients without incontinence, showed a significant improvement of symptoms and voided volume after 12 weeks of treatment (Abrams and swift, 2005).

  Comparison of the new (solifenacin, darifenacin) and old antimuscarinic agents showed the two generations of treatment had similar efficacy (Herbison et al., 2003).
A randomized, double-blind study, found that solifenacin is superior to an encapsulated formulation of tolterodine ER in most of the efficacy outcomes. The majority of side effects were mild to moderate in nature, yet significantly more for solifenacin, and discontinuations were comparable and low in both groups (Chapple et al., 2005).

In another, randomized, placebo-controlled study, Cardozo et al found that solifenacin significantly reduced the number of urgency episodes and urgency bother, and was well tolerated. Treatment was effective as early as day 3 (Cardozo et al., 2008).

Solifenacin is the first antimuscarinic to demonstrate significant warning-time (the time from first sensation of urgency to voiding) improvement in a large OAB clinical trial conducted to evaluate warning time and diary variables in the same study population (Karram et al., 2009).

A relatively recent comprehensive review for solifenacin concluded that this agent was effective in the treatment of OAB with urge incontinence (Maniscalco et al., 2006).

- Trospium:

Trospium chloride is a quaternary ammonium compound. It does not cross the blood–brain barrier; therefore no central nervous system adverse events are anticipated (Rovner, 2004). This drug significantly reduces urinary urge incontinence and frequency compared with placebo (Zinner et al., 2004).

Compared to tolterodine, trospium reduced the frequency of micturition and incontinence episodes. Extended-release trospium chloride 60mg, a novel modified–release form of this compound allows once-daily administration, potentially enhancing compliance to treatment
and improving its clinical efficacy/tolerability profile, compared with immediate-release form (Cardozo et al., 2010).

It was proved that the extent of metabolism of this drug is low and independent of the liver cytochrome P450 (CYP450) isoenzyme system. This pharmacodynamic profile further simplifies decision-making in polypharmacy situations, such as multi-morbid and elderly patients. Furthermore, subject to predominantly renal elimination as the unchanged form, trospium chloride retains its pharmacological activity within the urinary bladder, and local action on urothelium muscarinic receptors is supposed to contribute to its early onset and sustained efficacy in controlling urgency (Cardozo et al., 2010).

- **Fesoterodine**

Fesoterodine is one of the newest antimuscarinic for the treatment of OAB. Fesoterodine is a prodrug. It is rapidly and extensively hydrolyzed by nonspecific esterases, thus bypassing the CYP system, to 5-hydroxymethyl tolterodine (5-HMT), which is also the active metabolite of tolterodine. Interestingly, as 5-HMT formation from fesoterodine occurs via nonspecific esterases, the rate of fesoterodine hydrolyzation may be more uniform and complete. Initial data from phase 2 trials showed that fesoterodine was an effective and well-tolerated therapy for OAB (Nitti et al., 2005).

In subsequent clinical studies, fesoterodine doses of 4 and 8 mg/day were consistently superior to placebo in improving overactive bladder symptoms, with 8 mg/day having significantly greater effects than 4 mg/day (Michel, 2008). Both doses were safe and well tolerated,
with a low overall incidence of adverse events. Tolerability is comparable to that of tolterodine (ER) (Chaple et al., 2007).

Analysis of pooled data from two clinical trials including 1,548 women with overactive bladder, fesoterodine 4 mg and 8 mg and tolterodine showed significant improvements in all bladder diary variables assessed and greater response rates versus placebo. Fesoterodine 8 mg was significantly more efficacious than fesoterodine 4 mg and tolterodine ER in improving UUI episodes and continence days per week (Kaplan et al., 2010).

Recently, the FACT (Fesoterodine Assessment and Comparison Versus Tolterodine) study, a head–to–head placebo controlled trial, compared the efficacy and tolerability of fesoterodine 8 mg with tolterodine ER 4 mg. This study was designed to assess the superiority of fesoterodine over tolterodine ER for the treatment of OAB symptoms, and 1697 patients were included. This trial concluded that in patients with OAB, fesoterodine 8 mg showed superior efficacy over tolterodine ER 4 mg and placebo in reducing UUI episodes and in improving most patient-reported outcome measures. Both active treatments were well tolerated (Herschorn et al., 2010).

In another important study the flexible dose of fesoterodine was evaluated. Among 516 subjects treated, approximately 50% chose for dose escalation to 8 mg at week 4. The study concluded that flexible dose fesoterodine significantly improved OAB symptoms and rates of treatment satisfaction and was well tolerated in patients with OAB who were dissatisfied with prior tolterodine therapy (Wyndaele et al., 2009).
Safety and side effects of Antimuscarinics:

Anticholinergic medications are relatively safe, with side effects that result from muscarinic receptor blockade in other organs in the body, muscarinic receptors are not exclusively found in the urinary tract, but are also present in salivary glands (muscarinic M1 and M3 receptor subtypes), gastrointestinal smooth muscle (muscarinic M2 and M3 receptor subtypes), eyes (muscarinic M3 and M5 receptor subtypes), heart (muscarinic M2 receptor subtype), and brain (muscarinic M1, M3, M4, and M5 receptor subtypes). This widespread distribution of muscarinic receptors within the body is related to the commonly observed side-effects (Chapple et al., 2005).

The most common side effects are dry mouth, pruritus, and constipation; however, blurred vision, tachycardia, constipation, and urinary retention have also been reported (Chapple et al., 2008).

These drugs can also impair the central nervous system, causing mild (drowsiness, fatigue), moderate (restlessness, confusion), or severe effects (delirium, seizures, or cognitive impairment) (Kay and Ebinger, 2008).

In individuals who have a higher risk for cognitive dysfunction or delirium, such as elderly patients or those with mild to moderate dementia, the use of the larger quaternary amine, trospium chloride, or the selective M3 receptor agonist darifenacin should be considered for first-line therapy, because studies suggest that these medications may be less likely to impair mental function. If severe side effects are
encountered by the patient, switching to a different anticholinergic medication is advised (Scheife and Takeda, 2005).

Antimuscarinic discontinuation rates are high (70% to 90%), in part due to adverse effects, but also because of perceptions of lack of benefit or because the severity of symptoms requiring management is not sufficiently reduced. A combination of behavioral and drug therapy has been shown to be more effective than either treatment alone (D’Souza et al., 2008).

Absolute contraindications to using anticholinergic medications include narrow-angle glaucoma, intestinal obstruction, cardiac arrhythmia, and myasthenia gravis. Ultimately, establishing realistic and individualized treatment options is essential for all patients. When optimized, patients can expect a 43% to 70% reduction in their OAB and urge incontinence symptoms (Diokno et al, 2003).

**Non muscarinic drugs:**

Non muscarinic drugs may be used alone or in combination with an antimuscarinic drug, to treat OAB.

- **Desmopressin:**

  Desmopressin is a less commonly used but effective treatment option for patients with nocturia. As a synthetic analogue of arginine vasopressin, it enhances re-absorption of water in the kidneys, thus reducing urine output and nightly voids with a measurable improvement in sleep quality. Hyponatremia is the most serious side effect and can manifest as drowsiness, headache, confusion, anuria, or water
intoxication. To avoid these symptoms, patient’s serum sodium levels should be monitored closely when first starting this medication (van Kerrebroeck et al., 2007).

The drug is available as a “melt” (60 mcg or 120 mcg), a tablet (0.1 mg or 0.2 mg), or nasal spray. In 2008, Health Canada issued a warning that the desmopressin acetate nasal spray is contraindicated in primary nocturnal enuresis, due to risk of hyponatremia. It is now listed as “to be used with caution,” particularly in elderly patients who appear to be more predisposed to developing hyponatremia (Barkin, 2011).

• **Tricyclic antidepressants:**

  The tricyclic antidepressants imipramine (Tofranil) and amitriptyline (Elavil) are other non muscarinic drugs that may be used to treat OAB. Tricyclic antidepressants have a central sedating effect, relax the bladder walls, and through stimulation of alpha-adrenergic receptors, cause tightening of the sphincter, which may be helpful in some patients. This combination of effects may treat the symptoms of OAB and prevent urgency incontinence. Side effects may include fatigue, dry mouth, dizziness, blurred vision, nausea, and insomnia, and can also result in incomplete bladder emptying (partial retention). (Barkin, 2011).

**Specialized management:**

The International Consultation on Incontinence (ICI) guidelines state that when the first line approach is not fully satisfactory or fails after 8–12 weeks, alternative therapies should be sought out (Abrams et al, 2010).

It is worthwhile and justified to proceed to second-line therapy if patients are refractory to antimuscarinic therapy or if the treatment is
contraindicated. Second-line therapies include less-invasive measures such as detrusor injections with botulinum toxin and neuromodulation, whereas more-invasive measures constitute surgical techniques e.g. bladder augmentation or substitution.

Refractory OAB is generally investigated with urodynamics to define the underlying mechanisms, identify additional contributory factors and to detect potential risk factors for adverse treatment outcome.

**Neuromodulation:**

Neuromodulation is gaining support as a treatment for patients with refractory urge UI. This involves surgical implantation of an electronic device that stimulates the sacral nerves that modulate the bladder, sphincter, and pelvic floor muscles, of which all contribute to urge UI. (*Alan J et al 2006*).

Abrams et al reviewed pivotal data from a multicenter trial involving patients with urge UI, urinary retention, and/or refractory urgency and frequency. Sacral nerve stimulation was effective for a decrease of 50% or greater, or elimination of UI episodes in 76% of patients. (*Abrams, et al 2003*).

Neuromodulation is considered a viable strategic option to address either refractory OAB or idiopathic urinary retention after initial conservative therapy has failed. (*Abrams, et al 2003*)

The posterior tibial nerve is a peripheral mixed sensory motor nerve that originates from spinal roots L4 through S3, which also contribute directly to sensory and motor control of the urinary bladder and pelvic floor. Stimulation of the posterior tibial nerve was pioneered by Stoller and colleagues with the introduction of the Stoller afferent nerve stimulator which delivers electrical stimulation to the posterior tibial nerve via a 34-gauge needle just cephalad to the medial malleolus
(Cooperberg and Stoller, 2005). Encouraging initial experiments in pig-tailed monkeys led Marshall Stoller to describe a new technique, the Stoller Afferent Nerve Stimulations (SANS) in which an electric stimuli is applied percutaneously using an acupuncture needle inserted near the tibial nerve. Repeated electrical stimulation of this acupuncture point appeared to lengthen the interval between detrusor contractions. Stoller was able to document an 81% clinical success rate in 90 patients with a mean patient follow-up of 5.1 years (Stoller, 1999).

Neuromodulation has become popular since it bridges the gap between conservative treatment and highly invasive options. Currently, these devices include Sacral nerve modulation via surgically implanted electrodes, and newer methods that deliver percutaneous stimulation of the peripheral tibial nerve.

**Botulinum neurotoxin-A injection:**

It will be discussed in details.

**Reconstructive and invasive surgery:**

Bowel segments have been used in surgical management of intractable LUTS for many years (Young et al, 2003).

The main surgical procedure used in patients with severe refractory DO has been augmentation cystoplasty, in which the bladder is cut in half and the defect closed with a detubularized segment of intestine isolated from the rest of the bowel. Morbidity is considerable, and comparatively few patients with idiopathic DO are willing to contemplate the risks and potential adverse effects (Chapple and Bryan, 1998).
Urinary diversion—re-routing the ureters into a stoma derived from an isolated segment of intestine—can be undertaken in severe cases of OAB, after careful consideration and counseling. The evidence base for outcomes is very limited. (Young et al, 2003).

Detrusor myectomy, or auto-augmentation, is the excision of a substantial proportion of bladder muscle, leaving the bladder as a thin-walled reservoir with impaired contractility. Benefits have been reported in reducing the severity of DO-associated incontinence, but the outcomes in neurogenic DO can be disappointing due to symptom persistence and the technical difficulty of performing the procedure in the neuropathic bladder. The technique is not widely practiced (Kumar and Abrams, 2005).

Bladder distension and other denervation techniques aimed at limiting the sensory information reaching the CNS generally have poor long-term outcomes, and are no longer supported by expert consensus (Madersbacher, 2000).
History of Botulinum toxin:

Since botulinum neurotoxin was initially approved in 1989 by the U.S. Food and Drug Administration, it has become a powerful therapeutic tool in the treatment of a variety of neurologic, ophthalmic and other disorders. (Chancellor and Smith, 2011).

The use of botulinum toxin (BoNT) has expanded to include gastrointestinal, orthopedic, dermatologic, secretory, and cosmetic disorders. BoNT has also been applied in the clinical management of pain in a number of areas, including myofascial pain disorders, migraine headache, low back pain, and other chronic pain syndromes. Most exciting is the promising results of botulinum toxin use in a variety of genitourinary organs and lower urinary track dysfunctions. (Chancellor and Smith, 2011).

Botulinum neurotoxins are well known for their ability to potently and selectively disrupt and modulate neurotransmission. Only recently have urologists become interested in the potential use of BoNT in patients with detrusor overactivity and other urological disorders. (Chancellor and Smith, 2011).

Types of Botulinum Toxin:

Seven botulinum toxin serotypes (A, B, C [C1 and C2], D, E, F, and G) are produced by Clostridium botulinum, a gram-positive anaerobic bacterium. The clinical syndrome of botulism can occur following ingestion of contaminated food, from colonization of the infant gastrointestinal tract, or from a wound infection. Human botulism is caused mainly by types A, B, E, and (rarely) F. Types C and D cause toxicity only in animals. All of these serotypes inhibit acetylcholine release, although their intracellular target proteins, the characteristics of
their actions, and their potencies vary substantially. (Chancellor and Smith, 2011).

The various botulinum toxins possess individual potencies, and care is required to assure proper use and avoid medication errors. Recent changes to the established drug names by the FDA were intended to reinforce these differences and prevent medication errors. Approved BoNT-A formulations are onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA; the only approved BoNT-B formulation is rimabotulinumtoxinB. These agents are marketed under the brand names Botox_, Dysport_, Xeomin_, and Myobloc_ or Neurobloc_, respectively. (Chancellor, et al 2013)

**Mechanism of action:**

1- The effect on muscle neurotransmission

BoNT is synthesized as a biologically inactive single-chain polypeptide (molecular mass ~150 kDa) that is activated by proteolytic cleavage of the polypeptide chain into a 100-kDa heavy chain and a 50-kDa light chain linked by a disulfide bond (Aoki 2005). The heavy chain is involved in the binding of the neurotoxin into specific parts of the peripheral nervous system and in the transport of the neurotoxin into the neuronal cytosol, while the light chain is responsible for cleavage of the intracellular protein chain transporting acetylcholine vesicles into the synaptic cleft (Dolly et al. 1984).

BoNT, taken up into the nerve terminals, cleaves the SNARE proteins, preventing assembly of the fusion complex and thus blocking the release of Acetycholine (ACh), leading to relaxation of the muscle. BoNT-A cleaves synaptosome-associated proteins of 25 kDa (SNAP-25)
(Blasi et al. 1993), whereas BoNT-B cleaves vesicle-associated membrane protein (VAMP), also known as synaptobrevin. Injection of BoNT into a muscle reduces alpha motoneuron activity on the extrafusal muscle fibers. Muscle spindles are simultaneously inhibited by the toxin’s blockade of the motoneuron control of intrafusal fibers and by its subsequent reduction of afferent signaling, thereby reducing feedback to the motoneurons and other pathways to reduce muscle contraction.

2- The effect on Synapses and Neuropeptides

In preclinical studies, BoNT therapy also leads to altered afferent input to the central nervous system produced by the effect on muscle spindles. The release of substance P, a neuropeptide involved in neurogenic inflammation and the genesis of pain disorders, also requires the SNARE protein activity that is inhibited by BoNT (Aoki 2005).

In other preclinical studies, BoNT has also been shown to suppress the release of glutamate, another neurotransmitter involved in nociception in the periphery and in the dorsal horn of the spinal cord (Cui et al. 2004). Moreover, BoNT can reduce the release of other neurotransmitters (Ashton and Dolly 1988) and neuromediators, including epinephrine, norepinephrine, and calcitonin gene-related peptide.

While BoNT appears to have no direct central nervous system activity, its effects on the neuromuscular junction and muscle spindle organs may have indirect central nervous system effects. At the spinal level, BoNT produces reflex inhibition of motoneurons and subsequent afferent input suppression. On the supraspinal level, BoNT normalizes altered intracortical inhibition and somatosensory evoked potentials. Positron emission tomography scans of writer’s cramp patients treated
with BoNT found that treatment resulted in enhanced activation of parietal cortex and motor accessory areas but failed to improve the impaired activation of the primary motor cortex seen in the condition (Gilio et al. 2000).

3- The effect on urinary tract striated and smooth muscles

None of the clinically available Clostridial neurotoxins cause death of neurons or myocytes, or alteration of other cellular constituents. Thus, these neurotoxins are not toxic to tissues. Rather, in muscles, they act as biochemical neuromodulators, temporarily inactivating cholinergic transmission at the neuromuscular junction. Historically, the molecular mechanisms of BoNT have mostly been elucidated in studies of striated muscle. More recently, as a result of recognizing new clinical applications of BoNT, there have been studies conducted on the biological effects of BoNT on smooth muscle (Atiemo et al. 2005).

Despite some apparent differences at the cellular level, BoNT administration has the same clinical effect on both smooth and striated muscle. In the case of BoNT administration to the bladder wall, there is an increase in bladder capacity, with a reduction in incontinence episodes and symptoms of urgency. A more complete neuromuscular blockade of the detrusor results in impaired voiding and/or urinary retention if relatively larger doses of BoNT are used (Schurch et al. 2005).

4- The effect on efferent nerves

Smith and colleagues found significant decrease in the release of labeled acetylcholine in BoNT injected in normal rat bladders suggesting that BoNT could reduce cholinergic nerve induced bladder activity (Smith et al. 2003a) . Datta and associates (2010) recently demonstrated
decreased muscarinic receptor levels were restored back to control levels in the urothelium and suburothelium of patients successfully treated with BoNT for neurogenic and idiopathic detrusor overactivity.

5- The effect on afferent nerves

BoNT’s efficacy in conditions of detrusor overactivity may result not only from an inhibitory effect on detrusor muscle, but some effects of the drug may be mediated by altering afferent (sensory) input. (Hawthorn et al. 2000), recent basic and clinical evidence suggests that BoNT may have sensory inhibitory effects unrelated to its actions on acetylcholine release. (Khera et al. 2004). BoNT has also been shown to inhibit release of neuropeptides such as calcitonin generelated peptide, substances thought to play a role in overactive bladder conditions such as sensory urgency or chronic bladder inflammation (i.e., interstitial cystitis) (Rapp et al. 2006; Chuang et al. 2004).

6- Effects on Acetylcholine and ATP Release

ATP has also been implicated as a neurotransmitter in the generation of unstable contractions in idiopathic detrusor overactivity (Bayliss et al. 1999; O’Reilly et al. 2002). Studies on guinea pig (MacKenzie et al. 1982) and rat (Smith et al. 2003a) bladder strips have shown that BoNT is capable of inhibiting the release of both acetylcholine and ATP, providing a rationale for its possible use in treating patients with idiopathic overactive bladder. Bladder urothelium may play an important role in the sensory transduction mechanisms modulating micturition, particularly in conditions of increased sensory nerve transmission following chronic inflammation and spinal cord injury (Khera et al. 2004). Urothelial cells can release ATP (Birder et al. 2002), and the increased release of ATP from the urothelium of spinal cord injured rat
bladders could activate purine P2X3 receptors in epithelial and subepithelial layers to increase afferent nerve activity, accounting for the higher frequency of bladder contractions seen in both human and animal models of spinal cord injury.

BoNT was shown to inhibit ATP release from the urothelium but not the serosal side of the bladder, suggesting that BoNT treatment inhibits neurotransmitter release not only from efferent nerve endings but from sensory nerve terminals and/or urothelium as well (Khera et al. 2004). BoNT significantly impairs urothelial ATP release following spinal cord injury presents a plausible explanation for its clinical efficacy in the treatment of human neurogenic bladder dysfunction.

7- Effect on hot and cold sensitive sensory receptors

Originally described as a capsaicin receptor related to natural irritants (called vanilloids), the Transient Receptor Potential channel Vanilloid family member 1 (TRPV1) receptor is believed to function as an integrator of noxious stimuli, such as acids, heat, pollutants with a negative electronic charge, and endogenous pro-inflammatory substances. TRPV1 plays a key role in the perception of peripheral thermal and inflammatory pain (Morenilla-Palao et al. 2004). Recent findings indicate that BoNT blocks TRPV1 membrane translocation induced by protein kinase C, suggesting that activity-dependent delivery of channels to the neuronal surface may contribute to the buildup and maintenance of thermal inflammatory hyperalgesia in peripheral nociceptor terminals (Morenilla-Palao et al. 2004). Successful BoNT treatment for overactive bladder is associated with a significant decrease of TRPV1 and/or P2X3 in suburothelial nerve fibers (Apostolidis et al. 2005).
8- Effects on calcitonin gene-related peptide and substance P release

Sensory axons in the bladder contain both calcitonin gene-related peptide (CGRP) and substance P. These neuropeptides, which are released from nociceptive sensory endings in response to noxious stimuli, function as inflammatory response mediators (Basbaum and Jessell 2000).

Substance P acts on mast cells to produce degranulation, resulting in release of histamine and cytokines, which directly sensitize or excite nociceptors. In addition, both substance P and CGRP produce edema (substance P through plasma extravasation, and CGRP through dilation of peripheral blood vessels), causing liberation of bradykinin, all of which can lead to further activation of primary afferent fibers (Basbaum and Jessell 2000). Together with bradykinin and prostaglandins, substance P and CGRP also cause migration of leukocytes to the site of injury and clotting responses (Aoki 2005; Zubrzycka and Janecka 2000). BoNT has been shown in several preclinical models to block the release of CGRP, substance P, and glutamate from afferent nerve terminals (Aoki 2005; Chuang et al. 2004).

The effect of BoNT on sensory pathways is supported by results reported in preclinical models of bladder pain, in which intravesical application of BoNT significantly reduced pain responses and inhibited CGRP release from afferent nerve terminals, suggesting that BoNT may have clinical applications for the treatment of disorders such as interstitial cystitis and sensory urgency (Chuang et al. 2004; Rapp et al. 2006).

9- Inhibition of nerve growth factor release and receptor transport
In both animals and humans, the bladder increases production of nerve growth factor (NGF) in response to conditions such as spinal cord injury, denervation, inflammation, distension, or hypertrophy (Steers and Tuttle 2006).

It is produced in the smooth muscle of the urinary tract and urothelium of the bladder, and elevated NGF levels have been reported to trigger bladder overactivity, such as that seen in men with benign prostatic hyperplasia, women with interstitial cystitis, and in patients with idiopathic overactive bladder. Intravesical BoNT injection reduces nerve growth factor content in the bladder tissue of patients with neurogenic detrusor overactivity but it is unknown whether reduced bladder NGF results from decreased production, decreased uptake or a combination of both (Steers and Tuttle 2006).

The result of this action of BoNT is to decrease the hyperexcitability of C-fiber bladder afferents, thereby reducing neurogenic detrusor overactivity (Giannantoni et al. 2006).

**Histological changes after intra vesical injection**

Haferkamp et al. (2004) evaluated ultrastructural changes in overactive human detrusor tissue following BoNT injection in 30 biopsies from 24 patients with a diagnosis of neurogenic overactive bladder. Biopsies were taken before and 3 months after BoNT injection and during the wearing-off phase of the toxin’s efficacy. They observed no significant changes in muscle cell fascicles, intercellular collagen content or muscle cell degeneration when comparing biopsies taken before and after BoNT administration, although these results cannot be extrapolated to the possible structural effects of repeat injections. Unlike striated muscle, axonal sprouting in detrusor smooth muscle was limited
following BoNT administration, and further research is required to determine if prolonged toxin dosing will elicit such a response. The results of an immunohistochemical study also suggested no significant axonal sprouting in the suburothelium of successfully treated patients (Apostolidis et al. 2005).

An important study reported histopathological changes in excised human neurogenic overactive bladders that could be associated with intradetrusor BoNT injections. Full-thickness specimens from bladders previously treated with one or more injections of BoNT showed significantly less fibrosis, but no differences in inflammation and edema compared to untreated ones; degrees of inflammation, edema and fibrosis were comparable in the two groups. Treated bladders had been injected with a mean number of 1.5 ± 0.8 injections, and the mean time between the last injection and surgery was 6.8 ± 2.8 months (Comperat et al. 2006).

Although the majority of long-term results are positive, more data is needed from both smooth and striated muscle. A case study by Coletti Moja and colleagues has described acute neuromuscular failure in a patient who had a 2-year history of regular abobotulinumtoxinA treatment (800–1,000 U every 3 months for limb spasticity) (Coletti Moja et al. 2004).

Biopsy investigations showed subacute denervation and inflammation of the deltoid muscle with unspecified diffuse abnormalities of group II afferent fibers at a site distal to the area of drug administration, with clinical features resembling an acute myasthenic-like syndrome. Such findings indicate that there is still much to learn about the effects of long-term exposure to BoNT. (Coletti Moja et al. 2004).
BoNT Antibody Production

Questions remain about the long-term use of BoNT and the potential for development of resistance, with repeated treatments often leading to a progressive decline in therapeutic response. It has been suggested that this decline may be caused by development of neutralizing antibodies to BoNT. The functionally relevant antigenicity of a BoNT preparation depends upon the amount of botulinum toxin presented to the immune system, which is in turn determined by the specific biological activity and the relationship between the biological activity and the amount of botulinum neurotoxin contained in the preparation (Dressler and Hallett 2006).

It is important to remember that almost all of the published papers on the presence of antibodies have been based on use of the original onabotulinumtoxinA (Botox) formulation. The current formulation has a much lower protein load and a reduced incidence of antibody production. Is a clinical possibility, it is not a significant concern when considering the appropriate and safe use of the currently available formulations (with the possible exception of patients who may have had extended exposure to the original onabotulinumtoxinA formulation). It is important to note that if a patient does not respond to a particular injection, this does not necessarily indicate that the patient has developed blocking antibodies. In fact, the same patient may respond at a subsequent visit to exactly the same dose injected in the same muscles. (Chancellor and Smith, 2011).
Intravesical botulinum type-A toxin in the treatment of idiopathic detrusor overactivity

Common pharmacologic treatments to reduce bladder contractility include anticholinergics, antispasmodics, and tricyclic antidepressants. However, these therapies are associated with a high incidence of side effects including dry mouth, constipation and blurred vision, and often are not effective enough to reduce incontinence in cases of severe overactivity. Newer agents that target sensory fibers (e.g., capsaicin and resiniferatoxin) have shown early clinical promise although larger studies are still needed to judge the overall efficacy of this approach (Chancellor and de Groat 1999).

So, the only options available to patients who do not respond to or discontinue anticholinergic therapy are invasive procedures such as implantable devices to chronically stimulate the sacral nerve or surgical bladder augmentation. While these procedures may be effective for some patients, they are highly invasive, do not necessarily guarantee continence, and may have long term complications (Bosch 1998; Hohenfellner et al. 2000; Van Kerrebroeck et al. 1997).

Many studies have been carried out using botulinum neurotoxin (BoNT) in the treatment of patients who suffer from bladder overactivity. Suppression of involuntary detrusor contractions has been attempted via
the local administration of BoNT serotype A to the detrusor muscle, which inhibits acetylcholine release by cleaving SNAP 25, a protein integral to successful docking and release of vesicles within the nerve endings, including acetylcholine, calcitonin gene-related peptides (CGRP), glutamate and substance-P (Blasi et al. 1993; Cui et al. 2004; Meunier et al. 1996; Welch et al. 2000).

BoNT is believed to inhibit the acetylcholine-mediated detrusor contractions and may also inhibit other vesical-bound neurotransmitters in both the afferent and efferent pathways of the bladder wall, urothelium, or lamina propria (Chancellor et al. 2008).

**Technique of injection**

It should be emphasized that no standardized injection technique exists for BoNT injection in lower urinary tract tissues. For patients with idiopathic detrusor overactivity and OAB, onabotulinumtoxinA doses have ranged from 100 to 300 units. However, few controlled studies have been performed to determine the optimum dose or toxin dilution in idiopathic detrusor overactivity patient populations. Different injection paradigms have been described (i.e., trigone vs. trigone-sparing) although none has been proven to be superior to the other. In addition, fear of inducing vesicoureteral reflux with trigonal injection was disproven in a study by Karsenty and colleagues (Karsenty et al. 2007).

Bladder injections with BoNT can be made using either a rigid or flexible cystoscope, under general or local anesthesia.

The number of injections and volume of each injection given also vary widely. Such variability may affect the diffusion characteristics and efficacy of the treatment as well as the possibility of adverse events. Karsenty and associates prospectively randomized 24 neurogenic
patients to 300 U Botox over either 30 or 10 sites (Karsenty G, et al 2005).

They found no change in efficacy, safety, or QoL by a decrease in injection sites (increase in single-site bolus dose). This provides indirect evidence that a dose-dependent diffusion of BoNT-A activity occurs. This may allow the potential for using even fewer injection sites in the future, to further shorten and simplify the procedure. Controversy remains regarding the safety and usefulness of injecting the trigone. The concern is that injection near the ureteric orifices may lead to increased VUR, particularly in susceptible patients with NDO. Additionally the trigone has a rich submucosal sensory nerve plexus containing adrenergic, cholinergic, and nonadrenergic noncholinergic fibres. Injection here is postulated to therefore increase pain at the time of injection in awake patients, and the response to the neurotransmitter blockade by BoNT is unpredictable in such a complex plexus (Reitz, et al 2004). Conversely, the antinociceptive properties of BoNT may mean that the trigone is an ideal/important site for injection and there may be an argument to include the trigone in the injections (Harper, et al 2003).

Indeed Zermann et al, injected the trigone and bladder base in patients with severe urgency and frequency. No complications were reported and 57% of patients showed some improvement in frequency and bladder capacity. Due to the increased understanding of the role of the urothelium in overactive bladder (OAB) (Zermann et al, 2001).

Kuo et al. assessed suburothelial injections of BoNT. It was found that although this method of administration was more effective than detrusor injections, there was impaired bladder sensation and voiding efficiency.

Voiding difficulty was reported by 75% of patients and 30% required catheterisation. This suggests that blockade of detrusor
contractility through suburothelial sensory fibres was much more pronounced than at neuromuscular junctions or that only a small amount of diffusion of BoNT from the detrusor to the suburothelium occurs following detrusor injection, leading to the level of responses previously reported. (Kuo, et al, 2005).

**Trials on Botulium Toxin type A injection**

Sahai and colleagues detailed the first randomized placebo-controlled trial comparing the effect of 200 U of onabotulinumtoxinA versus saline bladder injection in 34 patients (i.e., 16 onabotulinumtoxinA and 18 placebo) with idiopathic detrusor overactivity and inadequately treated with 6 months of anticholinergic therapy (Sahai et al. 2007).

A total of 200 U of onabotulinumtoxinA was diluted in 20 ml of saline (i.e., 10 U/ml; or saline was used alone as placebo) and was injected in 20 places within the bladder wall, sparing the trigone. The primary endpoint measure was change in maximum cystometric capacity. OnabotulinumtoxinA improved maximum cystometric capacity significantly by 96 ml at 12 weeks. In addition, marked reductions in urinary frequency, and decreases in the number of urge urinary incontinence episodes and in the level of urgency was observed. The investigators also noted improvements in quality of life questionnaires in the onabotulinumtoxinA treated group.

Brubaker and associates compared the effects of 200 U of onabotulinumtoxinA versus saline bladder injections in 43 female patients with refractory urge urinary incontinence defined as >6 incontinence episodes/3 days and having failed at least two anticholinergic drugs (Brubaker et al. 2008). Patients were randomized in a 2:1 ratio: 28 patients received 200 U of onabotulinumtoxinA diluted in 6 ml of preservative free saline (i.e., 33 U/ml) and 15 patients received
saline injections alone. A total of 15–20 injections were placed in the posterior wall of the bladder sparing the trigone. The primary endpoint was time to failure, defined as a patient global impression of improvement score of 4 or greater 2 months after treatment. Sixty percent of patients treated with onabotulinumtoxinA demonstrated improvements in patient global impression of improvement score with a median duration of response of 373 days compared to 62 days or less for the placebo group. In addition, patients treated with onabotulinumtoxinA displayed greater than a 75% reduction in urge incontinence episodes by 3 day voiding diary. Unfortunately, the study was curtailed after recruiting 43 patients because 43% of patients treated with onabotulinumtoxinA required intermittent catheterization for a median duration of approximately 2 months.

Flynn and colleague evaluated the effect of two doses of onabotulinumtoxinA (i.e., 200 U and 300 U) versus placebo in 22 patients with refractory OAB defined as: greater than 2 daily urge incontinence episodes/day on a 3 day voiding diary, a 24 h pad weight of >100 g, and failure to respond to at least one anticholinergic medication (Flynn et al. 2009).

Candidates did not require urodynamically proven overactivity to be included in this study. The investigators were blinded to the dose of toxin given at the time of the study, thus the onabotulinumtoxinA results represent the combined results of both doses (i.e., 15 patients treated with onabotulinumtoxinA and 7 patients treated with placebo). The primary endpoints analyzed were the number of incontinence episodes/24 h and the quality of life and urinary distress questionnaire results. Interestingly, as opposed to the two prior studies, these investigators diluted onabotulinumtoxinA in only 3 ml (i.e., 66–100 U/ml) and injected the
bladder in 10–12 sites along the posterior bladder wall, sparing the trigone. At 6 weeks of follow-up, significant reductions in incontinence episodes/day were noted in the onabotulinumtoxinA treated group (i.e., 57.5%). In addition, marked improvements in quality of life and urinary distress symptoms scores were observed as well. Furthermore, pad weight decreased by 45% and the mean number of pads/day dropped from 4.4 to 2.2 pads/day. The largest and most recent randomized placebo-controlled study evaluated several doses of onabotulinumtoxinA (i.e., 50, 100, 150, 200, and 300 U) versus placebo in 313 patients with idiopathic OAB and urinary urge incontinence not adequately managed with anticholinergic medications (Dmochowski et al. 2010).

Patients had to experience at least eight urinary urge incontinence episodes/week and eight or more micturitions/day to be included in the study. The primary endpoint was weekly urinary urgency incontinence episodes at 12 weeks. Subjects were injected at 20 sites into the detrusor muscle (i.e., 0.5 ml/site) avoiding the trigone and the dome. The authors stated that significant difference from placebo was observed in the number of urgency incontinence episodes/week at many time points. However, they also stated that a clear dose response effect was not observed in regards to efficacy, although by non-parametric analysis minimal additional benefit was achieved by doses above 150 U of onabotulinumtoxinA. In contrast, a clear dose response relationship was displayed in the proportion of patients with a posttreatment residual urine volume of 200 ml or greater.

Anger and colleagues performed a meta-analysis of the three randomized, placebo controlled trials up to that time point using onabotulinumtoxinA in patients with idiopathic OAB (Anger et al. 2010). Pooled analysis of the three studies revealed that patients treated with onabotulinumtoxinA had almost four fewer episodes of urge urinary
incontinence per day than placebo treated patients. Their analysis also revealed that onabotulinumtoxinA treated patient’s demonstrated improved quality of life scores, estimated by a 15 point drop in urinary distress inventory (UDI-6) scores compared to placebo injected patients. However, the benefit from onabotulinumtoxinA was curbed by the nearly ninefold increase in the risk of elevated post-void residual urine volume in onabotulinumtoxinA treated patients compared to controls. A recent European expert panel report gave BoNT the highest grade level recommendation (i.e., grade A) for the treatment of refractory idiopathic detrusor overactivity (Apostolidis et al. 2009).
**Side effects:**

Many studies demonstrated significant dose-dependent improvements in urinary symptoms and urodynamic parameters in patients with OAB (Sahai et al., 2007, Kuo et al., 2007 – Dmochowski et al. 2009). However, the incidence of adverse events is also associated with increasing dose of BoNTA (Kuo 2006, Dmochowski et al 2009).

The main adverse events associated with BoNTA injection are acute urinary retention (AUR), large postvoid residual (PVR), difficulty in urination, and urinary tract infection (UTI), which occurred in approximately 20–43% of patients (Kessler et al, 2005, Kuo 2006, Sahai et al, 2007, Brubaker et al, 2008).

Large PVR after BoNTA injection was clinically relevant and clean intermittent catheterization (CIC) was necessary (Kuo, 2005, Kuo, 2006, Brubaker et al, 2008). In a recent report, complete continence after 200 U Botox injection was 51% at 4wk (Khan et al, 2010). Although patients without complete continence may experience improvement in urgency incontinence, they might not be satisfied with the treatment outcome due to these bothersome adverse effects. (Chancellor and Smith, 2011).

**Tachyphylaxis:**

Due to the antigenicity of BoNT, after repeat injections a small number of patients mount an immune response with the formation of neutralising antibodies. To minimise the small risk of BoNT resistance, most investigators currently recommend waiting at least 3 mo between
treatments, avoiding the use of booster injections and using the smallest
dose that achieves the desired clinical effect (Maria et al., 2005). The
newer formulation of Botox used after 1998 is thought to have drastically
reduced the occurrence of resistance (Rackley et al., 2004).

There have been a couple of case reports of the development of
resistance to BoNT -A with continued efficacy with therapy switch to
BoNT -B (Reitz and Schurch, 2004, Pistolesi et al, 2004). The
different target proteins for these toxins may explain the continuned efficacy
following the development of resistance to one serotype. However, the
presence of some cross reactive antibodies may limit this use. (Chancellor and Smith, 2011).
Anatomy of the urinary bladder

The urinary bladder is a hollow viscus with a strong muscular wall. It is characterized by its distensibility. It is a temporary reservoir and varies in size, shape, position and relations according to its content and the state of neighboring viscera. When empty, it lies entirely in the lesser pelvis but as it distends it expands antrosuperiorly into the abdominal cavity in some individuals, a full bladder may ascend to the level of umbilicus (Glass, 2005).

The bladder is located anterior to the vagina, uterus, and cervix in the female (figure 1), while in the male it is superior to the prostate and antroposterior to the seminal vesicles (figure 2). Antroinferiorly; the bladder is supported by the symphysis pubis. The space between the anterior bladder wall and the posterior aspect of the symphysis pubis is known as anterior perivesical space or space of Retzius (Moore et al, 2010).

Figure 1: median sagital section through female pelvis showing the urinary bladder relations. Quoted from (Glass,2005).
The bladder is made of smooth muscle (Detrusor muscle). It is adapted for mass contraction, not peristalsis. The muscle is lined by mucus membrane, surfaced by transitional epithelium. It has an approximate shape of a three-sized pyramid. There are two inferolateral surfaces cradled by anterior parts of levator ani, a neck where the urethra opens, and a superior surface, which is the one that most obviously moves when the bladder fills (Brooks, 2007).

When empty, the bladder is somewhat tetrahedral, and is described as having a superior surface with an apex at the urachus, two inferolateral surfaces which slopes downwards and medially to meet its fellow, lying against the front part of the pelvic diaphragm and obturator internus, and a base (fundus) of the bladder is the posteroinferior surface (Glass, 2005), with the bladder neck at the lowest point where the urethra opens (Brooks, 2007).
The apex: superoanterior portion of the bladder and it is relatively thin portion and is quite distensible. The vesical apex in both sexes faces towards the upper part of the symphysis pubis. The urachus anchors the bladder apex to the anterior abdominal wall. The urachus is composed of longitudinal smooth muscle bundles derived from the bladder wall. Near the umbilicus, it becomes more fibrous and usually fuses with the obliterated umbilical arteries. There are no hard and fast dividing lines between the various surfaces especially when distended (Brooks, 2007).

The base (fundus) of the bladder is the posteroinferior surface and it is triangular in shape. In females it is closely related to the anterior vaginal wall; in males it is related to the rectum although it is separated from it above by the rectovesical pouch and below by seminal vesicle and vas deferens on each side (Moore et al, 2010).

The trigone (figure 3) is a triangular area at the base of the bladder lying between the two ureteral orifices (above and laterally) and the internal urethral orifice (centrally and below). In the empty bladder, these three openings are 2.5 cm apart from each other but when distended, the uretral orifices may be 5 cm apart (Tanagho and McAninch, 2008).
Figure 3: Interior of the urinary bladder showing the trigone and its relations.

Quoted from (Glass, 2005).

In the triangular area between the vasa deferentia, the bladder and rectum are separated only by the rectovesical fascia, commonly known as Denonvillier’s fascia. The inferior part of this area may be obliterated by approximation of the ampullae of the vas deferens above the prostate (Glass, 2005).

The muscle of the trigone forms three distinct layers: 1- a superficial layer derived from the longitudinal muscle of the ureter, 2- a deep layer, and 3- a detrusor layer. The urothelium overlying the muscular trigone is usually only three cells thick and adherent strongly to the underlying muscle by a dense lamina propria. During filling and emptying of the bladder, this mucosal surface remains smooth. (Brooks, 2007).
The neck is the lowest region and is also the most fixed. It is 3-4 cm behind the lower part of the symphysis pubis, which is a little above the plane of the inferior aperture of the lesser pelvis. Toward the neck of the male bladder, the muscle fibers form the involuntary internal urethral sphincter. This sphincter contracts during ejaculation to prevent retrograde ejaculation (figure 4) (Moore et al, 2010).

![Bladder neck and sphincter of the urinary bladder](image)

Figure 4: bladder neck and sphincter of the urinary bladder

Quoted from (Moore et al, 2010).

This sphincter is not a true circular sphincter but a thickening formed by interlaced and covering muscle fibers of the detrusor as they pass distally to become the smooth muscle of the urethra (Tanagho and McAninch, 2008).

In males the neck rests on, and in direct continuity with the base of the prostate; in females it is related to the pelvic fascia, which surrounds the upper urethra (Tanagho, 2008).
In males the superior surface of the urinary bladder is covered by *peritoneum* *(figure 5)*. Anteriorly, the peritoneum sweeps gently on to the anterior abdominal wall with distention; the bladder rises out of the true pelvis and separates the peritoneum from the anterior abdominal wall. Posteriorly, the peritoneum, passes to the level of the seminal vesicles and meets the peritoneum on the anterior rectum to form the rectovesical space *(Brooks, 2007)*.

![Figure 5: Relations of peritoneum to the bladder and rectum. The arrow points to the rectovesical pouch. Quoted from (Glass, 2005).](image)

In the female *(figure 6)*, the peritoneum on the superior surface of the bladder is reflected over the uterus to form the vesicouterine pouch and then extends posteriorly over the uterus as rectouterine pouch.

In infants, the true pelvis is shallow and the bladder neck is level with the upper border of the symphysis. The bladder is a true intra-abdominal organ that can project above the umbilicus when full. By puberty, the bladder has migrated to the confines of the deepened true pelvis. *(Brooks, 2007)*
Figure 6: The peritoneum covering the female urinary bladder.

*Quoted from (Moore et al, 2010).*
Endoscopic Anatomy of Urinary Bladder

The mucosa is formed of transitional epithelial cells that flatten and form a single epithelial layer during bladder distension. In the distensible portions of the bladder, the mucosa is only loosely attached to the submucosa but is more firmly attached directly to the muscular layer over the trigone. It remains smooth in this area regardless of the state distension since the trigonal area does not distend. In the distensible areas, the mucosal pattern can be related to the degree of filling. The mucosa appears flat when the bladder is filled but can appear redundant or wrinkled when the bladder contains a lesser volume. The normal bladder mucosa is pale, cream red in colour showing small blood vessels radiating and branching underneath (Reuter, 1987).

![Fig.7: conventional cystoscopy reveals normal appearing mucosa.](image-url)
Points of orientation are the bladder neck with the trigone and ureteric orifices, in one hand, and bladder roof on the other hand (Reuter, 1987).

The bladder neck, which limits the bladder interiorly and distally, appears as a funnel-shaped opening of the urethra into the bladder. Endoscopically, the bladder neck is seen when the instrument passes proximally into the bladder. From that point, the bladder neck appears as a concentric muscular ring. The bladder neck remains the major landmark and reference point in the anatomy of the bladder when viewed from the superior aspect, either with the bladder opened or with an endoscopy placed through a suprapubic tract.

The trigone is formed of two muscle layers superimposed on the detrusor muscle. The superficial trigone is formed as a direct continuation of fibres in the roof and the floor of the intravesical ureter. The deep trigone is formed by direct continuation of Waldeyer's sheath, a fibromuscular structure that completely encircles the distal 3 to 4 cm of the juxtavesical ureter and follows the ureter through the ureteral canal. The sheath (now the deep trigone) continues under the superficial trigone. The trigone and the dense ventral condensation, the middle circular layer of the detrusor, surround the bladder outlet (Tanagho, 2008).
The trigone is subjected to many variations with respect to the position of ureteric orifices, its surface area, and angulation. In the male, it frequently extends with several longitudinal urethral folds as far as the verumontanum. Its mucosa is velvety and more strongly colored than that of the remaining bladder; there are no muscular markings of any kind (including spastic or pathologic ones, such as in trabeculation) (Reuter, 1987).

The interureteric ridge is an elevation extending between the ureteral orifices. It is more prominent in males than females, in whom it may, be poorly defined. The ureteral orifices are located along the interureteric ridge symmetrically, usually 1 to 2cm from the midline. There is great variation in the appearance of the normal ureteral orifice. In the adult, a normal, nonrefluxing orifice may have the configuration described as a volcano, a horseshoe, slit-like or some other variation. The orifice may either be quite prominent and obvious
on endoscopic examination or appear as a slit distinguishable from the surrounding mucosa only through careful inspection. The ureteral orifice is often surrounded by a characteristic mucosal vascular pattern. Prominent mucosal vessels course in an arc medial, inferior, and lateral to the orifice. This pattern is often obscured in the presence of generalized mucosal inflammation (Tanagho, 2008).

The base or the fundus of the bladder is located posterior to the trigone. The lateral walls of the bladder extend superiorly to the dome or vertex, as do the anterior and posterior walls. The normal vascular pattern and topographic appearance of the mucosa can be seen over the bladder musculature in these areas (Fig 7). When the bladder is distended, this pattern becomes relatively smooth unless there is prominent trabeculation (Bagley et al., 1985).
Neuroanatomy and neurophysiology of the lower urinary tract

The main function of the lower urinary tract is to store and expel urine. The urinary bladder is a hollow organ with strong muscular wall, the detrusor muscle, which functions as a reservoir. When empty, the bladder is entirely located within the pelvis. As it fills, it can contain about 500 cc or more while it rises into the abdominal cavity. The bladder neck, urethra and pelvic floor form the bladder outlet and facilitate urine evacuation. From both sides the ureters penetrate the bladder in its posterolateral wall after tunneling the bladder wall obliquely over a 1-2 cm long to end as the ureteral orifices. The posterolateral angles formed by the ureters orifices and the internal orifice of the urethra form a triangular area: trigone (Groat, 1993).

The bladder is composed of four layers: serous, muscular, submucosal and mucosal layers. The tunica mucosa is continuous with the lining membrane of the ureters and renal pelvis, and below with that of the proximal urethra. The areolar tissue of the tunica submucosa connects the mucosa only slightly; it makes the bladder look wrinkled when contracted. Over the trigone the mucous membrane is firmly attached to the muscular coat, and thus looks smooth and flat. The tunica muscularis consists of three layers. The internal longitudinal layer is thin; fibers are organized for the most part in a longitudinal direction. In the middle layer, the fibers are irregularly scattered, but circularly arranged toward the lower part forming a thick circular sphincter vesicae around the urethral orifice. The external layer has been named
the detrusor muscle and is composed of fibers organized in a longitudinal arrangement. The outer tunica serosa is derived from the peritoneum (Gray, 1995).

The physiological internal sphincter maintains continence by closure of the bladder neck and proximal urethra. Continence is thought to be dependent on a combination of urethral wall tension, the caliber of the urethral lumen and the functional length. The striated muscles surrounding the urethra are not only essential for urinary continence but are also important in the voluntary termination of urine flow and prevention of stress incontinence (Steers, 1998).

INNERVATION:

Storage and expulsion of urine is the result of complex neural network interactions. Different neural circuits located in brain, brain stem, spinal cord and peripheral nerves and ganglia regulate bladder filling and coordinated micturation. Interaction of somatic and autonomic efferent signals, voluntary on-off control mechanism and learned behaviour modulate the lower urinary tract’s function (Boron and Boulpaep, 2003).

Neural circuits controlling storage and expulsion of urine

Filling of the bladder and voiding involve a complex pattern of afferent and efferent signaling in parasympathetic (pelvic nerves), sympathetic (hypogastric nerves), and somatic (pudendal nerves) pathways. These pathways constitute reflexes, which either keep the
bladder in a relaxed state, enabling urine storage at low intravesical pressure, or initiate bladder emptying by relaxing the outflow region and contracting detrusor (Andersson, 2008)

PARASYMPATHETIC PATHWAYS

The sacral parasympathetic pathways mediate contraction of the detrusor smooth muscle and relaxation of the outflow region. The preganglionic parasympathetic neurons are located in the sacral parasympathetic nucleus (SPN) in the spinal cord at the level of S2–S4. The axons pass through the pelvic nerves and synapse with the postganglionic nerves in either the pelvic plexus, in ganglia on the surface of the bladder (vesical ganglia), or within the walls of the bladder and urethra (intramural ganglia). The ganglionic neurotransmission is predominantly mediated by acetylcholine acting on nicotinic receptors, although the transmission can be modulated by adrenergic, muscarinic, purinergic, and peptidergic presynaptic receptors. The postganglionic neurones in the pelvic nerve mediate the excitatory input to the normal human detrusor smooth muscle by releasing acetylcholine acting on muscarinic receptors. However, an atropine-resistant (nonadrenergic, noncholinergic: NANC) contractile component is regularly found in the bladders of most animal species. Such a component can also be demonstrated in functionally and morphologically altered human bladder tissue, but contributes only to a few percent to normal detrusor contraction (O’Reilly, 2002).

Adenosine triphosphate (ATP) is the most important mediator of the NANC contraction, although the involvement of other transmitters cannot be ruled out. (Andersson and Wein, 2004).
Substances acting as neurotransmitters or neuromodulators include an extensive list, e.g., opioids, vasoactive intestinal polypeptide (VIP), serotonin, dopamine, glutamic acid, GABA, ATP, and prostaglandins (F2, E, E2). Many of these substances exhibit both inhibitory and facilitative influence on the micturition cycle at the spinal cord level and higher (Klarskov et al., 1984).

The pelvic nerve also conveys parasympathetic nerves to the outflow region and the urethra. These nerves exert an inhibitory effect on the smooth muscle, by releasing nitric oxide and other transmitters. (Andersson and Wein, 2004).

SYMPATHETIC PATHWAYS

The sympathetic innervation of the bladder and urethra originates from the intermediolateral nuclei in the thoracolumbar region (T11–L2) of the spinal cord. The axons leave the spinal cord via the splanchnic nerves and travel either through the inferior mesenteric ganglia (IMF) and the hypogastric nerve, or pass through the paravertebral chain to the lumbosacral sympathetic chain ganglia and enter the pelvic nerve. Thus, sympathetic signals are conveyed in both the hypogastric nerve and the pelvic nerve. The ganglionic sympathetic transmission is, like the parasympathetic preganglionic transmission, predominantly mediated by acetylcholine acting on nicotinic receptors. Some preganglionic terminals synapse with the postganglionic cells in the paravertebral ganglia or in the IMF, while other synapse closer to the pelvic organs, and short postganglionic neurones innervate the target organs. Thus, the hypogastric and pelvic nerves contain both pre- and postganglionic fibre. The predominant effect of the sympathetic innervation is to contract the bladder.
base and the urethra. In addition, the sympathetic innervation inhibits the parasympathetic pathways at spinal and ganglionic levels. In the human bladder, noradrenaline is released in response to electrical stimulation in vitro, and the normal detrusor response to released noradrenaline is relaxation. However, the importance of the sympathetic innervation for relaxation of the human detrusor has never been established. In contrast, in several animal species the adrenergic innervation has been demonstrated to mediate relaxation of the detrusor during filling. (Andersson and Arner, 2004).

The smooth muscle of the bladder and proximal urethra in a variety of animals and in humans contains both α- and β-adrenergic receptors. α-adrenergic contractile responses predominate in the bladder base and proximal urethra, whereas β-adrenergic relaxation responses predominate in the bladder body (Wein and Moy, 2007).

SOMATIC PATHWAYS

The somatic innervation of the urethral rhabdosphincter and of some perineal muscles (eg, compressor urethrae and urethrovaginal sphincter) is provided by the pudendal nerve. These fibers originate from sphincter motor neurons located in the ventral horn of the sacral spinal cord (levels S2–S4) in a region called Onuf’s (Onufrowicz’s) nucleus (Thor and Donatucci, 2004).

AFFERENT PATHWAYS

Afferent axons in the pelvic, hypogastric, and pudendal nerves transmit information from the lower urinary tract to the lumbosacral spinal cord. (Yoshimura and de Groat, 1997).
The primary afferent neurons of the pelvic and pudendal nerves are contained in sacral dorsal root ganglia (DRG), whereas afferent innervation in the hypogastric nerves contained in the rostral lumbar DRG. The central axons of the DRG neurons carry the sensory information from the lower urinary tract to second-order neurons in the spinal cord (de Groat et al, 1996). Visceral afferent fibers of the pelvic and pudendal nerves enter the cord and travel rostrocaudally within Lissauer's tract (Thor et al, 1989).

The most important afferents for the micturition process are myelinated Aδ-fibers and unmyelinated C-fibers traveling in the pelvic nerve to the sacral spinal cord, conveying information from receptors in the bladder wall. The Aδ-fibers respond to passive distension and active contraction, thus conveying information about bladder filling. The activation threshold for Aδ-fibers is 5–15 mm H2O. This is the intravesical pressure at which humans report the first sensation of bladder filling. C-fibers have a high mechanical threshold and respond primarily to chemical irritation of the bladder urothelium/suburothelium or to cold. Following chemical irritation, the C-fiber afferents exhibit spontaneous firing when the bladder is empty and increased firing during bladder distension. These fibers are normally inactive and are therefore termed “silent fibers.” Afferent information about the amount of urine in the bladder is continuously conveyed to the mesencephalic periaqueductal gray (PAG), and from there to the pontine micturition center (PMC), also called Barrington’s nucleus. (Holstege, 2005; Kuipers et al., 2006).

NORMAL STORAGE

Urine storage involves the bladder’s ability to accommodate increasing volume of urine at a low intravesical pressure. This
relationship is a measure of normal bladder compliance (C) \( C = \frac{\Delta \text{Volume}}{\Delta \text{detrusor Pressure}} \). Effective urine storage requires the bladder outlet to remain closed at rest and during increased intra-abdominal pressure (Wein, 2007).

Afferent signals from the pudendal and pelvic nerves activate the sacral and pontine micturition centers to stimulate increased sphincter tone and decrease parasympathetic detrusor contraction. Sympathetic nerves act to increase urethral resistance during this bladder filling process. Additionally, voluntary squeezing of the sphincter can decrease urinary urgency by activating the inhibitory reflex arc (Tanagho, 2008).

NORMAL VOIDING

Coordinated voiding similarly involves the sacral and pontine micturition centers. The micturition reflex coordinates the interaction between the detrusor muscle and urethral sphincter. The activation of the micturition reflex occurs in response to the stimulation of tension receptors and nociceptors in the bladder wall caused by bladder distension (Wein, 2007).

Bladder afferent nerve impulses travel to the sacral cord triggering detrusor contraction, bladder neck and sphincter relaxation. The cycle of micturition is then initiated by the relaxation of the striated urethral sphincter and the pelvic floor muscles. This results in a decrease in the urethral pressure. The bladder then contracts, and this increase in detrusor pressure results in urine flow as the intravesical pressure equals and then exceeds the intraurethral pressure (Blaivas, 1985).

Normally, the brain stem modulates the reflex such that the bladder contraction is appropriately sustained to allow for complete emptying. Following voiding, the detrusor muscle receives efferent
inhibitory signals and the intraurethral pressure increases as the striated urethral sphincter contracts to again allow for storage of urine (Blaivas, 1985).

Figure 9
Storage and voiding reflexes of the bladder. (Hassouna et al., 2008)
The Overactive bladder

Definition:
Overactive bladder (OAB) is defined as a symptom complex comprising urinary urgency, with or without urgency incontinence, usually with frequency and nocturia in the absence of pathological or metabolic disorders (Abrams et al., 2002).

Urgency is the hallmark of OAB, and is defined as the sudden compelling desire to urinate which is difficult to defer. OAB is a clinical diagnosis, distinct from the diagnosis made on urodynamic assessment of detrusor overactivity (DO). The overlap between urodynamically-defined DO and subjectively-reported OAB is substantial, but many people with OAB do not have DO and people with DO do not always have urgency (Hashim and Abrams, 2006).

Prevalence:

The prevalence of OAB increases with age. From the epidemiological studies conducted to date, it can be concluded that of those patients with OAB, approximately one-third are troubled by incontinence (OAB ‘wet’) and two-thirds are not (OAB ‘dry’). The NOBLE (National Overactive Bladder Evaluation) study estimated the overall prevalence of this condition in the US population to be 16% in men and 16.9% in women. As the population ages, an overall increase in prevalence occurs (Stewart et al., 2003).

A Japanese epidemiological survey estimated a slightly lower overall incidence (12.4%) in the general population aged over 40, but the prevalence increased with age, with more than 20% of people older than 70 years and more than 35% older than 80 suffering lower urinary tract symptoms (Homma et al., 2003).
More available data from the EPIC (European Prospective Investigation into Cancer and Nutrition) Study suggest that the prevalence of OAB symptoms (using the 2002 International Continence Society (ICS) definition) is closer to 12% in the community; and of these sufferers, approximately 50% experience significant bother from their symptoms (Irwin et al., 2006).

Abdelwahab and his colleagues in 2011 in their study on Outcomes of the urogenital distress inventory (UDI-6) for 20- to 50-year-old females with lower urinary tract dysfunction in Qalubia Governorate, Egypt, urge incontinence was present in 22.2% of patients. The presence of mild and moderate stress incontinence and mild urge incontinence increased significantly in patients who were 41-50 years old. Micturition difficulty and micturition frequency occurred in < 7% of patients (Abdelwahab et al., 2011).

**Pathophysiology:**

The exact cause of idiopathic OAB is not well defined. Several theories regarding the etiology of OAB have been proposed:

- **Neurogenic Theory:**

The neurogenic theory states that detrusor overactivity arises from generalized, nerve-mediated excitation of the detrusor muscle. There are several interdependent mechanisms by which this may arise. **First,** damage to the brain can induce detrusor overactivity by reducing suprapontine inhibition. **Second,** damage to axonal pathways in the spinal cord allows the expression of primitive spinal bladder reflexes. **Third,** synaptic plasticity leads to reorganization of sacral activity, with the emergence of new reflexes, which may be triggered by C-fiber bladder
afferent neurons. **Finally**, sensitization of peripheral afferent terminals in the bladder can trigger detrusor overactivity ([de Groat, 1997](#)).

- **Increased myogenic activity of detrusor smooth muscles:**

  This is an important mechanism inducing OAB and detrusor overactivity, which seems to be more applicable to patients with bladder outlet obstruction (BOO). Partial BOO increases intravesical pressure and induces bladder hypertrophy and partial denervation of the bladder smooth muscle, leading to various functional changes in smooth muscles. These changes include denervation supersensitivity of cholinergic (muscarinic) receptors, increases in purinergic receptor–mediated contractile responses as well as expression of purinergic receptors such as P2X1 ([Boselli et al., 2001](#)), and changes in the cell-to-cell communication in detrusor muscles due to up-regulation of gap-junction proteins such as connexin. Thus, increases in receptor-mediated muscle contractility and interaction between smooth muscles cells can result in coordinated myogenic contraction of the entire bladder and detrusor overactivity ([Haferkamp et al., 2004](#)).

  It has been suggested that local contraction (activity) that occurs somewhere in the detrusor will spread throughout the bladder wall, resulting in coordinated myogenic contraction of the whole bladder. This local contraction in the bladder wall has been shown to generate afferent discharge ([Drake et al., 2005](#)).

  Localized bladder activity was assessed by the micro-motion detection method, demonstrating that women with increased bladder sensation on filling cystometry had a significantly higher prevalence of localized activity than the control group. This observation suggests that localized distortion of the bladder wall simulates afferent activity which
would precipitate a feeling of urgency and detrusor overactivity (Drake et al., 2005).

In addition, another population of cells in the bladder known as interstitial cells has been proposed for a pace-making role in spontaneous activity of the bladder. Because it has been reported that the number of interstitial cells is increased in a guinea-pig model of BOO (Kubota et al., 2007) and that c-kit tyrosine kinase inhibitors, which inhibit interstitial cell activity, decreased the amplitude of spontaneous contractions in the guinea-pig and human bladder, interstitial cells may also be involved in the emergence of detrusor overactivity because of enhanced autonomous detrusor muscle activity (Biers et al., 2006).

- **Role of non-neuronal Ach and the muscarinic receptors:**

  Recently, new evidence suggests an increased release of acetylcholine (Ach) during urine storage, both from neuronal and non-neuronal (including urothelium) sources. The release can be enhanced by distension of the bladder and increases with advancing age, and it appears to contribute to the pathophysiology of OAB (Andersson, 2011).

  Ach is the main contractile transmitter in the human bladder. It is released from postganglionic efferent cholinergic (parasympathetic) nerves, acts on muscarinic receptors, and produces the contraction that empties the bladder (Giglio, 2009).

  However, there is also a non-neuronal release of ACh that may be involved in other bladder functions. Recent studies analyzed the content of ACh in the urothelium and characterized the molecular components of its synthesis and release machinery. They found ACh to be present in the urothelium in a nanomolar range per gram of wet weight. This means that the urothelium is a source of ACh, it also implies that muscarinic
receptors within the urothelium and underlying structures can be targets for antimuscarinic drugs (Lips, 2007).

It may be assumed that during the storage phase, there is an ongoing release of ACh from nerves or from a non-neurogenic source, possibly the urothelium. ACh may then act indirectly, by release of other mediators, or directly on afferent nerves to initiate the micturition reflex or enhance the myogenic (spontaneous) contractile activity of the detrusor. This activity seems to be increased in patients with DO, in turn increasing “afferent noise” (Andersson, 2010).

There is normally no parasympathetic outflow from the spinal cord during filling. Nevertheless, the bladder maintains a “tone” and exhibits non synchronized local contractions and relaxations, and this is believed to be caused by a myogenic contractile activity that is reinforced by release of mediators from non-neuronal (urothelium, lamina propria, other structures) as well as neuronal sources. There are reasons to believe that the spontaneous contractile phasic activity of the detrusor smooth muscle during filling can generate afferent input “afferent noise” and that in pathologic conditions (e.g., OAB), this input may contribute to these disorders (Gillespie, 2009).

Finally, there may be a combined etiology secondary to an abnormal leak of acetylcholine that cause micro-motions in the bladder smooth muscle, which in turn stimulates the CNS, leading to the sensation of urgency (Andersson, 2004).

**Symptomatology:**

Symptoms of bladder overactivity as defined by ICS (Abrams et al, 2002):
• **Increased day time frequency:** is the complaint of voiding too often by day.

• **Nocturia:** is the complaint that the individual has to wake at night one or more times to void.

• **Urgency:** is the complaint of sudden compelling desire to pass urine which is difficult to defer.

• **Urge incontinence:** is the complaint of involuntary leakage of urine accompanied by or immediately preceded by urgency.

**Risk Factors:**

Risk factors most commonly associated with OAB and incontinence include age 75 years and older, arthritis, chronic lung disease, depression, diminished cognitive status and delirium, fecal impaction, hysterectomy, immobility, increased BMI in women, diabetes, lumbar disk disease, multiple vaginal deliveries, stroke, urinary tract infection, vaginal or bladder surgery, and white race. Individuals taking alpha-adrenergic blockers, alpha-adrenergic agonists, anticholinergics, antimuscarinics, antidepressants, antipsychotics, beta-adrenergic agonists, calcium channel blockers, diuretics, hormone replacement therapy, hypnotics, and/or sedatives are also at increased risk of developing OAB symptoms (Rosenberg and Dmochowski, 2005).

**Co morbidities:**

OAB has a negative effect on quality of life. Patients limit their fluid intake, avoid sexual intimacy, wear pads and map the location of toilets also depression, sleep deprivation, urinary tract infections, skin infections, and orthopedic injuries resulting from falls related to OAB (Rosenberg and Dmochowski, 2005).
Diagnosis and Evaluation:

Initial evaluation of lower urinary tract symptoms suggestive of OAB typically includes a history, physical examination, urine analysis, and bladder diary evaluation is designed to rule out medical and non-medical etiologies for lower urinary tract symptoms, such as functional impairments, medication side effects, urinary tract infections, bladder outlet obstruction, bladder tumors, or neurologic etiologies, such as stroke or multiple sclerosis. In most individuals, a diagnosis of OAB can be made based on these components, and treatment can be started (Starkman and Dmochowski, 2008).

Symptomatic diagnosis of OAB does not correlate with a urodynamic diagnosis of detrusor instability. The diagnosis of overactive bladder based on urinary symptoms underdiagnoses the condition of detrusor instability in a population of women suffering from lower urinary tract symptoms. Therefore, symptomatic diagnosis of OAB alone is not recommended (Digesu et al., 2003).

Urodynamic testing is not required for an initial diagnosis of OAB. An increasing body of evidence suggests that, although there is a relationship between the urodynamic finding of detrusor overactivity and OAB, these are quite separate findings, and successful response to nonsurgical and surgical interventions for OAB does not depend on finding detrusor overactivity on urodynamic testing. The role of urodynamics in the setting of OAB is not well defined at present, but there are several clinical scenarios where such testing may be useful. However, at this time, the evidence to support their routine use in patients with OAB is limited (Rovner and Goudelocke , 2010).
Urodynamic evaluation should be done only if it is going to change patient treatment or help differentiate the etiology of voiding dysfunction, or if it is done after failed conservative/medical treatment (Colli et al, 2003).

Figure 10

a) Urodynamic chart in a case of OAB with detrusor overactivity.

b) Urodynamic chart in a case of OAB without detrusor overactivity (Colli et al, 2003)

Differential diagnosis:

Distinguishing OAB from common cause of urgency should be made. Urine analysis can easily exclude urinary tract infection as a common cause of lower urinary tract symptoms. Blood glucose level can exclude frequency due to diabetes mellitus. Old age patients suspicious of having malignancy are candidates for pelvi-abdominal ultrasonography.
which can also exclude – in combination with digital rectal examination – the presence of prostatomegaly in male patients.

The major disorder to be differentiated from OAB is painful bladder syndrome which is defined as the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased day-time and night-time frequency, in the absence of proven urinary infection or other obvious pathology therefore, as the key symptom of OAB urgency is defined as the complaint of a sudden compelling desire to pass urine, which is difficult to defer (for fear of leakage), then the key symptom of PBS is bladder pain. (Abrams et al., 2005).

When discussing symptoms with patients it can help to discuss the differences in sensation between the two conditions. In PBS, sensation builds to discomfort and then to pain and is felt suprapubically even if the patient also has perineal (urethral/vaginal/penile) discomfort/pain. In OAB, urgency is usually described as being felt lower down than the sensations of bladder filling and the normal desire to void. In men it is felt in the perineum/base of penis and in women in the vagina/urethra. (Abrams et al, 2005).

In OAB, urgency incontinence occurs in 50% of patients. In PBS, incontinence is uncommon although a small number of patients experiencing severe pain will voluntarily pass (‘‘leak’’) urine onto a pad or even into their underwear because they know that the reduction of bladder capacity, by even 10ml, will significantly reduce their pain: this is not urgency incontinence. Similarly, their pain does not give urgency (for fear of leakage) and it is perhaps better to say that they have a ‘‘desperate desire to void because of pain and fear of worsening pain’’. (Abrams et al., 2005).
In PBS, voided volumes are habitually small; both by day and by night, and a frequency volume chart should be completed to document the extent of the patient’s symptoms and the degree to which voided volumes are reduced. Most PBS patients will have a consistent voided volume below 250 ml. Occasional PBS patients have little frequency because they severely restrict their fluid intake and may sometimes avoid suffering nocturia by this maneuver (Abrams et al., 2005).
**Quality-of-Life Issues in Incontinence**

*1-Impact of urinary incontinence on health related quality of life*

Although urinary incontinence is traditionally thought of as a condition that affects quality of life, there are few studies that quantify the impact of this health problem on general health related quality of life. However, the studies that have been performed clearly demonstrate that this condition has a broad effect on quality of life. Using the Nottingham Health Profile, Grimby and his colleagues (Grimby, et al 1993) measured general HRQOL in 120 elderly women (mean age 75.4 years) with urinary incontinence. As a comparison group, 313 age-matched women without urinary incontinence also completed the questionnaire. They found that incontinent women experienced greater emotional disturbance and social isolation than the age-matched controls.

In another study, Haggland et al (Haglund, et al 2001) used a population-based approach to assess the impact of stress and urge incontinence on HRQOL in Surahammar, Sweden. HRQOL data were available in 596 women without incontinence, 440 women with stress incontinence, and 71 women with urge incontinence. Incontinent women, regardless of type, reported significantly lower general HRQOL scores in all eight domains of the SF-36. However, when stratified by type of incontinence, women with urge incontinence reported significantly worse general HRQOL in all domains even when compared to women with...
stress incontinence. The magnitude of difference in general HRQOL scores between women with stress, as opposed to urge, incontinence was particularly striking, 10–20 points lower in all domains, and underscore the clinical importance of these findings. Similarly, Hunskaar and Visnes used the Sickness Impact Profile to specifically compare women with urge incontinence to those with stress incontinence and found that the group with urge incontinence had significantly worse HRQOL in the sleep and social interaction domains of the SIP. In addition, they divided their cohort by age, comparing HRQOL in 36 incontinent women aged 40–60 years and 40 women age 70 years, while controlling for type of incontinence. Younger women had worse HRQOL than older women, particularly in the domains of emotional behavior and effect on recreation and pastimes. This study demonstrates that the effect of incontinence on general HRQOL is affected not only by the type of incontinence but also by the age of the patient. Interestingly, it is not simply incontinent episodes that affect quality of life in urge incontinence.

In a telephone study of overactive bladder (OAB), (O’Connor, et al 1998) Liberman and colleagues administered the SF-36 to 483 subjects with OAB symptoms and 191 controls. After adjusting for age, sex, and use of medical care, subjects with incontinent OAB (n ¼ 185) had worse HRQOL in the physical function, role-functional, bodily pain, health perceptions, social functioning, and mental health domains of the SF-36 when compared to controls. However, in the subgroup of patients with overactive bladder symptoms and no incontinence (n ¼ 298), significantly lower HRQOL scores were still noted in the role-functioning, mental health, health perception, and bodily pain domains. The investigators further divided this population into continent OAB patients with frequency only (n ¼ 175), urgency only (n ¼ 80), and both
frequency and urgency symptoms (n = 43). Of these three subgroups, only patients with continent OAB who experience both frequency and urgency have significant lower HRQOL scores than controls. This association was noted in all domains except for social function. This study and others (O’Conor, et al 1998) indicate that, while much of the quality of life impact of urge incontinence is due to the actual leakage episodes, the combination of frequency and urgency symptoms, in and of itself, also affects quality of life (Nirit, et al 2005).

Furthermore, in the 230 subjects who reported urinary incontinence, lower domain scores in physical and mental health, life satisfaction, and the perception that incontinence interfered with daily life were significant predictors of depression. (Dugan, et al 2000)

Other studies have found a similar relationship between urinary incontinence and depression and social isolation (Melville, et al 2002, Fultz, et al 2001).

In conclusion, urinary incontinence and lower urinary-tract symptoms appear to impact health related quality of life extensively, affecting physical, psychological, and emotional domains to a greater degree than clinicians might expect (Nirit, et al 2005).

2-Impact of incontinence treatment on health related quality of life

Given the broad impact of urinary incontinence on health-related quality of life as described above, it is important that we document that treatment for urinary incontinence result in improved quality of life for our patients. Although the field of health-related quality-of-life research in urinary incontinence is still young, several authors have used validated

**QoL Assessment**

There is many validated questionnaires used for evaluating QOL effect on patients with OAB as: EQ-5D and SF-36.

**EQ-5D:** The EQ-5D consists of two parts: the health states descriptive system and the visual analog rating scale (VAS). The descriptive system records the level of self-reported problems on each of the five dimensions of the classification (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). For each dimension the respondent is asked to choose between three options: no problem, some/moderate problems, or extreme problems/unable. Health states defined by the five-dimensional descriptive system can be converted into a weighted health state index by applying scores from value sets elicited from general population samples (Kind, 2003).

Respondents then describe their own health status using a VAS. A 20-cm vertical VAS has become the standard means of obtaining valuations for health states. The endpoints of the VAS are labeled “best imaginable health state” and “worst imaginable health state” anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health state by drawing a line from an anchor box to that point on the VAS that best represents their own health on that day (Brooks, 1996).

UK English, Spanish, and German versions have been adapted culturally and translated (Rabin and de Charro, 2001).
**SF-36:** The Medical Outcomes Trust Short Form 36- Item Health Survey (SF-36) is a generic measure of functional status and well-being. (Ware, et al 1993).

It contains 36 questions that measure health across eight dimensions—physical functioning (PF), role limitations because of physical health (RP), role limitation because of emotional health (RE), social functioning (SF), bodily pain (BP), mental health (MH), vitality or energy (VT), and general health perception (GH). Responses to each question within a dimension are combined to generate a score from 0 to 100, where 100 indicate “good health” and 0 indicates “poor health.” (Ware, et al 1993).
Management of Overactive Bladder

The International Consultation on Incontinence (ICI) algorithms divides management into initial treatment and specialized therapy (Abrams et al., 2010).

A combination of both behavioral and pharmacological therapy is considered to be the standard of care for the initial control of OAB symptoms; however, treatment strategies should be tailored according to the patient’s needs and expectations, and management goals should be shared with patients with an emphasis on controlling the symptoms and not curing the underlying condition. (Abrams et al., 2010).

The treatment mainly aims to reduce the sensation of urgency, increase the voided volume, reduce frequency, and eliminate leakage episodes. If OAB symptoms fail to be controlled by these measures, sacral nerve stimulation (SNS) or any other form of neuromodulation can be introduced to alleviate patient symptoms. If sacral neuromodulation proves to be ineffective, surgery is the last option that can be offered to these patients. (Abrams et al., 2010).

Behavioral therapy:

Components of behavioral therapy include education, timed voiding, delayed voiding, dietary modifications, and pelvic floor muscle exercises.

Behavioral therapy starts with education. Patients need to be educated regarding normal bladder function and normal voiding habits. Timed voiding involves voiding at set intervals, regardless of the urge to void, which may help to decrease the risk of urinary urge incontinence (UII) and urgency (Wyman, 2009).
In some individuals, caffeinated, spicy, and acidic foods and drinks may exacerbate symptoms, and thus, dietary restrictions may lead to improvement in symptoms. Normalizing fluid intake may also prove helpful; too much or even too little fluid may exacerbate symptoms because concentrated urine may act as a bladder irritant (Dallosso et al., 2004).

Individuals suffering from urgency and frequency, but not incontinence, may benefit from urgency suppression techniques and delayed voiding, which involves trying to hold urine for progressively longer periods of time by consciously suppressing the urge to void, as well as tightening pelvic floor muscles. Pelvic floor muscle exercises may also help decrease urgency and incontinence when properly performed. A bladder diary is useful in behavioral therapy because it allows patients to track their responses and identify possible factors that exacerbate their symptoms (Miller and Sand, 2007).

**Pharmacotherapy:**

**Antimuscarinics:**

There are a number of pharmacological mechanisms that could reduce overactivity of the detrusor muscle. However, antimuscarinic drugs are approved treatment as Grade A recommendation. (Andersson et al., 2009).

Antimuscarinics are the primary medical treatment for OAB of all ages. They exert their biological effects by competitively binding to the muscarinic receptors on the detrusor muscle (M2 and M3 subtypes), thereby preventing acetylcholine’s positive effects on contractility. They have been shown to reduce micturition frequency, urge incontinence episodes, and nocturia (Chapple et al., 2008).
Oxybutynin, Tolterodine, propiverine, solifenacin, darifenacin, trospium and fesoterodine are antimuscarinic agents approved for use in OAB treatment.

- **Oxybutynin:**

  Oxybutynin is the first antimuscarinic used for the treatment of OAB. In addition to its antimuscarinic action, Oxybutynin in high doses exerts muscle relaxant and local anesthetic effects (Siddiqui et al., 2004).

  Oxybutynin is now available in oral, immediate (IR) and extended-release (ER), as well as two transdermal formulations, a patch and a gel. An intravesical formulation of Oxybutynin has also been studied (Hanawa et al., 2008).

  Oxybutynin IR formulation was the first that entered clinical practice. Despite its satisfactory efficacy, the substantial incidence of dry-mouth, immediate release oxybutynin’s most common and bothersome side-effect, limited its tolerability. Newer formulations aimed at eliminating peaks in concentration of Oxybutynin and its metabolites in order to reduce related side-effects (Siddiqui et al., 2004).

  The ER formulation of Oxybutynin provides a smooth plasma concentration profile over the 24-hour dosage interval, facilitating once-daily administration. Hence, given its overall efficacy/tolerability and dose flexibility, Oxybutynin ER provides an alternative in the first-line of pharmacotherapy for OAB (Siddiqui et al., 2004).

  Overall, as shown in the OPERA (Overactive bladder: Performance of Extended Release Agents) study, Oxybutynin ER has modestly greater efficacy than tolterodine IR at its most commonly prescribed dose (Diokno et al., 2003).
In the OBJECT (Overactive Bladder Judging Effective Control and Treatment) study oxybutynin ER was more effective than tolterodine at the endpoints of urge incontinence, total incontinence, and micturition frequency episodes (Appell et al., 2001).

The transdermal oxybutynin (OXY-TDS) formulation offers patients with urinary incontinence an effective, safe and well-tolerated option for managing the symptoms of overactive bladder (Sand et al., 2007). As OAB contributes to decreased work productivity due to job interruptions as well as fatigue, the use of transdermal oxybutynin may result in productivity improvement when patients receive 3.9 mg/day via twice weekly patch application for up to 6 months (Pizzi et al., 2009).

Oxybutynin chloride topical gel (OTG) was approved in January 2009 by the US FDA. OTG was designed to provide steady plasma oxybutynin levels with daily application, favorably altering the circulating N-desethyloxybutynin metabolite to oxybutynin ratio, thus minimizing the antimuscarinic adverse effects of oral formulations. The use of a biocompatible delivery system also reduced the application-site skin reactions associated with other available forms of transdermal delivery. OTG represents an efficacious, safe, and convenient alternative to other oxybutynin formulations and oral antimuscarinics for the treatment of OAB (Staskin et al., 2009).

Interestingly, all the above mentioned oxybutynin formulations have been shown to be more efficacious than the IR oxybutynin in respective trials (Novara et al., 2008).

- **Tolterodine:**

  Tolterodine is a widely prescribed antimuscarinic and it was the first specifically developed to treat OAB. Tolterodine is not selective for
any muscarinic receptor subtype but it exhibits selectivity for the urinary bladder over salivary glands in vivo (Nilvebrant et al., 1997).

An IR formulation was available first, but an ER, administered once-daily, formulation was later designed. Its efficacy and tolerability have been proved in a large number of trials. Tolterodine offers significant improvement in overactive bladder symptoms and quality of life while having a favorable safety profile. It soon became the gold-standard in the class, a drug that all others are compared to, during their clinical development (Salvatore et al., 2008).

Oxybutynin and tolterodine, most commonly prescribed antimuscarinics, have been shown to have similar efficacies in general OAB populations, as well as in specific subpopulations defined by severity of urodynamic findings (Giannitsas et al., 2004).

- **Propiverine:**

  Propiverine, another muscarinic receptor antagonist, has also been demonstrated to inhibit L-type Ca++ channels in high concentrations (Madersbacher and Murtz, 2001).

  Propiverine has similar efficacy to oxybutynin and tolterodine, similar tolerability and impact on quality of life to tolterodine, but a better tolerability profile than oxybutynin. This drug is well tolerated (Junemann et al., 2005).

  Propiverine and oxybutynin are efficacious in children with incontinence due to overactive bladder and propiverine is officially approved in certain countries for pediatric use. Alloussi et al. evaluated existing evidence for the use of antimuscarinics in children. They
concluded that high-quality studies are still limited and results vary widely across antimuscarinics. (Alloussi et al., 2010).

The daily urgency episodes were significantly reduced from baseline to 12 weeks on propiverine treatment, compared with placebo. Secondary endpoints, including sum of urgency severity per 24 h, urgency severity period, and daytime voiding frequency, were also improved significantly in the propiverine group (Lee et al., 2010).

- **Darifenacin**

  Darifenacin is the antimuscarinic with the highest M3 receptor subtype selectivity. Long-term darifenacin treatment was associated with significant and clinically meaningful improvements in quality of life of patients with urge incontinence (“wet” OAB) over 2 years (Dwyer et al., 2008).

  In a study of patients who were dissatisfied with their previous treatment with oxybutynin ER or tolterodine ER, Patients OAB symptoms were significantly improved, and satisfaction was high during treatment with darifenacin 7.5 or 15 mg (Zinner et al., 2008).

- **Solifenacin**

  A pooled analysis of four randomized, placebo-controlled, phase III studies of solifenacin in OAB patients without incontinence, showed a significant improvement of symptoms and voided volume after 12 weeks of treatment (Abrams and swift, 2005).

  Comparison of the new (solifenacin, darifenacin) and old antimuscarinic agents showed the two generations of treatment had similar efficacy (Herbison et al., 2003).
A randomized, double-blind study, found that solifenacin is superior to an encapsulated formulation of tolterodine ER in most of the efficacy outcomes. The majority of side effects were mild to moderate in nature, yet significantly more for solifenacin, and discontinuations were comparable and low in both groups (Chapple et al., 2005).

In another, randomized, placebo-controlled study, Cardozo et al. found that solifenacin significantly reduced the number of urgency episodes and urgency bother, and was well tolerated. Treatment was effective as early as day 3 (Cardozo et al., 2008).

Solifenacin is the first antimuscarinic to demonstrate significant warning-time (the time from first sensation of urgency to voiding) improvement in a large OAB clinical trial conducted to evaluate warning time and diary variables in the same study population (Karram et al., 2009).

A relatively recent comprehensive review for solifenacin concluded that this agent was effective in the treatment of OAB with urge incontinence (Maniscalco et al., 2006).

- **Trospium:**

Trospium chloride is a quaternary ammonium compound. It does not cross the blood–brain barrier; therefore no central nervous system adverse events are anticipated (Rovner, 2004). This drug significantly reduces urinary urge incontinence and frequency compared with placebo (Zinner et al., 2004).

Compared to tolterodine, trospium reduced the frequency of micturition and incontinence episodes. Extended-release trospium chloride 60mg, a novel modified-release form of this compound allows once-daily administration, potentially enhancing compliance to treatment.
and improving its clinical efficacy/tolerability profile, compared with immediate-release form (Cardozo et al., 2010).

It was proved that the extent of metabolism of this drug is low and independent of the liver cytochrome P450 (CYP450) isoenzyme system. This pharmacodynamic profile further simplifies decision-making in polypharmacy situations, such as multi-morbid and elderly patients. Furthermore, subject to predominantly renal elimination as the unchanged form, trospium chloride retains its pharmacological activity within the urinary bladder, and local action on urothelium muscarinic receptors is supposed to contribute to its early onset and sustained efficacy in controlling urgency (Cardozo et al., 2010).

- **Fesoterodine**

  Fesoterodine is one of the newest antimuscarinic for the treatment of OAB. Fesoterodine is a prodrug. It is rapidly and extensively hydrolyzed by nonspecific esterases, thus bypassing the CYP system, to 5-hydroxymethyl tolterodine (5-HMT), which is also the active metabolite of tolterodine. Interestingly, as 5-HMT formation from fesoterodine occurs via nonspecific esterases, the rate of fesoterodine hydrolyzation may be more uniform and complete. Initial data from phase 2 trials showed that fesoterodine was an effective and well-tolerated therapy for OAB (Nitti et al., 2005).

  In subsequent clinical studies, fesoterodine doses of 4 and 8 mg/day were consistently superior to placebo in improving overactive bladder symptoms, with 8 mg/day having significantly greater effects than 4 mg/day (Michel, 2008). Both doses were safe and well tolerated,
with a low overall incidence of adverse events. Tolerability is comparable to that of tolterodine (ER) (Chaple et al., 2007).

Analysis of pooled data from two clinical trials including 1,548 women with overactive bladder, fesoterodine 4 mg and 8 mg and tolterodine showed significant improvements in all bladder diary variables assessed and greater response rates versus placebo. Fesoterodine 8 mg was significantly more efficacious than fesoterodine 4 mg and tolterodine ER in improving UUI episodes and continence days per week (Kaplan et al., 2010).

Recently, the FACT (Fesoterodine Assessment and Comparison Versus Tolterodine) study, a head–to–head placebo controlled trial, compared the efficacy and tolerability of fesoterodine 8 mg with tolterodine ER 4 mg. This study was designed to assess the superiority of fesoterodine over tolterodine ER for the treatment of OAB symptoms, and 1697 patients were included. This trial concluded that in patients with OAB, fesoterodine 8 mg showed superior efficacy over tolterodine ER 4 mg and placebo in reducing UUI episodes and in improving most patient-reported outcome measures. Both active treatments were well tolerated (Herschorn et al., 2010).

In another important study the flexible dose of fesoterodine was evaluated. Among 516 subjects treated, approximately 50% chose for dose escalation to 8 mg at week 4. The study concluded that flexible dose fesoterodine significantly improved OAB symptoms and rates of treatment satisfaction and was well tolerated in patients with OAB who were dissatisfied with prior tolterodine therapy (Wyndaele et al., 2009).
Safety and side effects of Antimuscarinics:

Anticholinergic medications are relatively safe, with side effects that result from muscarinic receptor blockade in other organs in the body; muscarinic receptors are not exclusively found in the urinary tract, but are also present in salivary glands (muscarinic M1 and M3 receptor subtypes), gastrointestinal smooth muscle (muscarinic M2 and M3 receptor subtypes), eyes (muscarinic M3 and M5 receptor subtypes), heart (muscarinic M2 receptor subtype), and brain (muscarinic M1, M3, M4, and M5 receptor subtypes). This widespread distribution of muscarinic receptors within the body is related to the commonly observed side-effects (Chapple et al., 2005).

The most common side effects are dry mouth, pruritus, and constipation; however, blurred vision, tachycardia, constipation, and urinary retention have also been reported (Chapple et al., 2008).

These drugs can also impair the central nervous system, causing mild (drowsiness, fatigue), moderate (restlessness, confusion), or severe effects (delirium, seizures, or cognitive impairment) (Kay and Ebinger, 2008).

In individuals who have a higher risk for cognitive dysfunction or delirium, such as elderly patients or those with mild to moderate dementia, the use of the larger quaternary amine, trospium chloride, or the selective M3 receptor agonist darifenacin should be considered for first-line therapy, because studies suggest that these medications may be less likely to impair mental function. If severe side effects are
encountered by the patient, switching to a different anticholinergic medication is advised (Scheife and Takeda, 2005).

Antimuscarinic discontinuation rates are high (70% to 90%), in part due to adverse effects, but also because of perceptions of lack of benefit or because the severity of symptoms requiring management is not sufficiently reduced. A combination of behavioral and drug therapy has been shown to be more effective than either treatment alone (D’Souza et al., 2008).

Absolute contraindications to using anticholinergic medications include narrow-angle glaucoma, intestinal obstruction, cardiac arrhythmia, and myasthenia gravis. Ultimately, establishing realistic and individualized treatment options is essential for all patients. When optimized, patients can expect a 43% to 70% reduction in their OAB and urge incontinence symptoms (Diokno et al, 2003).

**Non muscarinic drugs:**

Non muscarinic drugs may be used alone or in combination with an antimuscarinic drug, to treat OAB.

- **Desmopressin:**

  Desmopressin is a less commonly used but effective treatment option for patients with nocturia. As a synthetic analogue of arginine vasopressin, it enhances re-absorption of water in the kidneys, thus reducing urine output and nightly voids with a measurable improvement in sleep quality. Hyponatremia is the most serious side effect and can manifest as drowsiness, headache, confusion, anuria, or water
intoxication. To avoid these symptoms, patient’s serum sodium levels should be monitored closely when first starting this medication (van Kerrebroeck et al., 2007).

The drug is available as a “melt” (60 mcg or 120 mcg), a tablet (0.1 mg or 0.2 mg), or nasal spray. In 2008, Health Canada issued a warning that the desmopressin acetate nasal spray is contraindicated in primary nocturnal enuresis, due to risk of hyponatremia. It is now listed as “to be used with caution,” particularly in elderly patients who appear to be more predisposed to developing hyponatremia (Barkin, 2011).

- **Tricyclic antidepressants:**

  The tricyclic antidepressants imipramine (Tofranil) and amitriptyline (Elavil) are other non muscarinic drugs that may be used to treat OAB. Tricyclic antidepressants have a central sedating effect, relax the bladder walls, and through stimulation of alpha-adrenergic receptors, cause tightening of the sphincter, which may be helpful in some patients. This combination of effects may treat the symptoms of OAB and prevent urgency incontinence. Side effects may include fatigue, dry mouth, dizziness, blurred vision, nausea, and insomnia, and can also result in incomplete bladder emptying (partial retention). (Barkin, 2011).

**Specialized management:**

The International Consultation on Incontinence (ICI) guidelines state that when the first line approach is not fully satisfactory or fails after 8–12 weeks, alternative therapies should be sought out (Abrams et al, 2010).

It is worthwhile and justified to proceed to second-line therapy if patients are refractory to antimuscarinic therapy or if the treatment is
contraindicated. Second-line therapies include less-invasive measures such as detrusor injections with botulinum toxin and neuromodulation, whereas more-invasive measures constitute surgical techniques e.g. bladder augmentation or substitution.

Refractory OAB is generally investigated with urodynamics to define the underlying mechanisms, identify additional contributory factors and to detect potential risk factors for adverse treatment outcome.

**Neuromodulation:**

Neuromodulation is gaining support as a treatment for patients with refractory urge UI. This involves surgical implantation of an electronic device that stimulates the sacral nerves that modulate the bladder, sphincter, and pelvic floor muscles, of which all contribute to urge UI. (Alan J et al 2006).

Abrams et al reviewed pivotal data from a multicenter trial involving patients with urge UI, urinary retention, and/or refractory urgency and frequency. Sacral nerve stimulation was effective for a decrease of 50% or greater, or elimination of UI episodes in 76% of patients. (Abrams, et al 2003).

Neuromodulation is considered a viable strategic option to address either refractory OAB or idiopathic urinary retention after initial conservative therapy has failed. (Abrams, et al 2003)

The posterior tibial nerve is a peripheral mixed sensory motor nerve that originates from spinal roots L4 through S3, which also contribute directly to sensory and motor control of the urinary bladder and pelvic floor. Stimulation of the posterior tibial nerve was pioneered by Stoller and colleagues with the introduction of the Stoller afferent nerve stimulator which delivers electrical stimulation to the posterior tibial nerve via a 34-gauge needle just cephalad to the medial malleolus.
Encouraging initial experiments in pig-tailed monkeys led Marshall Stoller to describe a new technique, the Stoller Afferent Nerve Stimulations (SANS) in which an electric stimuli is applied percutaneously using an acupuncture needle inserted near the tibial nerve. Repeated electrical stimulation of this acupuncture point appeared to lengthen the interval between detrusor contractions. Stoller was able to document an 81% clinical success rate in 90 patients with a mean patient follow-up of 5.1 years (Stoller, 1999).

Neuromodulation has become popular since it bridges the gap between conservative treatment and highly invasive options. Currently, these devices include Sacral nerve modulation via surgically implanted electrodes, and newer methods that deliver percutaneous stimulation of the peripheral tibial nerve.

**Botulinum neurotoxin-A injection:**

It will be discussed in details.

**Reconstructive and invasive surgery:**

Bowel segments have been used in surgical management of intractable LUTS for many years (Young et al, 2003).

The main surgical procedure used in patients with severe refractory DO has been augmentation cystoplasty, in which the bladder is cut in half and the defect closed with a detubularized segment of intestine isolated from the rest of the bowel. Morbidity is considerable, and comparatively few patients with idiopathic DO are willing to contemplate the risks and potential adverse effects (Chapple and Bryan, 1998).
Urinary diversion—re-routing the ureters into a stoma derived from an isolated segment of intestine—can be undertaken in severe cases of OAB, after careful consideration and counseling. The evidence base for outcomes is very limited. (Young et al, 2003).

Detrusor myectomy, or auto-augmentation, is the excision of a substantial proportion of bladder muscle, leaving the bladder as a thin-walled reservoir with impaired contractility. Benefits have been reported in reducing the severity of DO-associated incontinence, but the outcomes in neurogenic DO can be disappointing due to symptom persistence and the technical difficulty of performing the procedure in the neuropathic bladder. The technique is not widely practiced (Kumar and Abrams, 2005).

Bladder distension and other denervation techniques aimed at limiting the sensory information reaching the CNS generally have poor long-term outcomes, and are no longer supported by expert consensus (Madersbacher, 2000).
**History of Botulinum toxin:**

Since botulinum neurotoxin was initially approved in 1989 by the U.S. Food and Drug Administration, it has become a powerful therapeutic tool in the treatment of a variety of neurologic, ophthalmic and other disorders. *(Chancellor and Smith, 2011).*

The use of botulinum toxin (BoNT) has expanded to include gastrointestinal, orthopedic, dermatologic, secretory, and cosmetic disorders. BoNT has also been applied in the clinical management of pain in a number of areas, including myofascial pain disorders, migraine headache, low back pain, and other chronic pain syndromes. Most exciting is the promising results of botulinum toxin use in a variety of genitourinary organs and lower urinary track dysfunctions. *(Chancellor and Smith, 2011).*

Botulinum neurotoxins are well known for their ability to potently and selectively disrupt and modulate neurotransmission. Only recently have urologists become interested in the potential use of BoNT in patients with detrusor overactivity and other urological disorders. *(Chancellor and Smith, 2011).*

**Types of Botulinum Toxin:**

Seven botulinum toxin serotypes (A, B, C [C1 and C2], D, E, F, and G) are produced by Clostridium botulinum, a gram-positive anaerobic bacterium. The clinical syndrome of botulism can occur following ingestion of contaminated food, from colonization of the infant gastrointestinal tract, or from a wound infection. Human botulism is caused mainly by types A, B, E, and (rarely) F. Types C and D cause toxicity only in animals. All of these serotypes inhibit acetylcholine release, although their intracellular target proteins, the characteristics of
their actions, and their potencies vary substantially. (Chancellor and Smith, 2011).

The various botulinum toxins possess individual potencies, and care is required to assure proper use and avoid medication errors. Recent changes to the established drug names by the FDA were intended to reinforce these differences and prevent medication errors. Approved BoNT-A formulations are onabotulinumtoxinA, abobotulinumtoxinA, and incobotulinumtoxinA; the only approved BoNT-B formulation is rimabotulinumtoxinB. These agents are marketed under the brand names Botox_, Dysport _, Xeomin_, and Myobloc_ or Neurobloc_, respectively. (Chancellor et al. 2013)

Mechanism of action:

1- The effect on muscle neurotransmission

BoNT is synthesized as a biologically inactive single-chain polypeptide (molecular mass ~150 kDa) that is activated by proteolytic cleavage of the polypeptide chain into a 100-kDa heavy chain and a 50-kDa light chain linked by a disulfide bond (Aoki 2005). The heavy chain is involved in the binding of the neurotoxin into specific parts of the peripheral nervous system and in the transport of the neurotoxin into the neuronal cytosol, while the light chain is responsible for cleavage of the intracellular protein chain transporting acetylcholine vesicles into the synaptic cleft (Dolly et al. 1984).

BoNT, taken up into the nerve terminals, cleaves the SNARE proteins, preventing assembly of the fusion complex and thus blocking the release of Acetycholine (ACh), leading to relaxation of the muscle. BoNT-A cleaves synaptosome-associated proteins of 25 kDa (SNAP-25)
(Blasi et al. 1993), whereas BoNT-B cleaves vesicle-associated membrane protein (VAMP), also known as synaptobrevin. Injection of BoNT into a muscle reduces alpha motoneuron activity on the extrafusal muscle fibers. Muscle spindles are simultaneously inhibited by the toxin’s blockade of the motoneuron control of intrafusal fibers and by its subsequent reduction of afferent signaling, thereby reducing feedback to the motoneurons and other pathways to reduce muscle contraction.

2- The effect on Synapses and Neuropeptides

In preclinical studies, BoNT therapy also leads to altered afferent input to the central nervous system produced by the effect on muscle spindles. The release of substance P, a neuropeptide involved in neurogenic inflammation and the genesis of pain disorders, also requires the SNARE protein activity that is inhibited by BoNT (Aoki 2005).

In other preclinical studies, BoNT has also been shown to suppress the release of glutamate, another neurotransmitter involved in nociception in the periphery and in the dorsal horn of the spinal cord (Cui et al. 2004). Moreover, BoNT can reduce the release of other neurotransmitters (Ashton and Dolly 1988) and neuromediators, including epinephrine, norepinephrine, and calcitonin gene-related peptide.

While BoNT appears to have no direct central nervous system activity, its effects on the neuromuscular junction and muscle spindle organs may have indirect central nervous system effects. At the spinal level, BoNT produces reflex inhibition of motoneurons and subsequent afferent input suppression. On the supraspinal level, BoNT normalizes altered intracortical inhibition and somatosensory evoked potentials. Positron emission tomography scans of writer’s cramp patients treated
with BoNT found that treatment resulted in enhanced activation of parietal cortex and motor accessory areas but failed to improve the impaired activation of the primary motor cortex seen in the condition (Gilio et al. 2000).

3- The effect on urinary tract striated and smooth muscles

None of the clinically available Clostridial neurotoxins cause death of neurons or myocytes, or alteration of other cellular constituents. Thus, these neurotoxins are not toxic to tissues. Rather, in muscles, they act as biochemical neuromodulators, temporarily inactivating cholinergic transmission at the neuromuscular junction. Historically, the molecular mechanisms of BoNT have mostly been elucidated in studies of striated muscle. More recently, as a result of recognizing new clinical applications of BoNT, there have been studies conducted on the biological effects of BoNT on smooth muscle (Atiemo et al. 2005).

Despite some apparent differences at the cellular level, BoNT administration has the same clinical effect on both smooth and striated muscle. In the case of BoNT administration to the bladder wall, there is an increase in bladder capacity, with a reduction in incontinence episodes and symptoms of urgency. A more complete neuromuscular blockade of the detrusor results in impaired voiding and/or urinary retention if relatively larger doses of BoNT are used (Schurch et al. 2005).

4- The effect on efferent nerves

Smith and colleagues found significant decrease in the release of labeled acetylcholine in BoNT injected in normal rat bladders suggesting that BoNT could reduce cholinergic nerve induced bladder activity (Smith et al. 2003a). Datta and associates (2010) recently demonstrated
decreased muscarinic receptor levels were restored back to control levels in the urothelium and suburothelium of patients successfully treated with BoNT for neurogenic and idiopathic detrusor overactivity.

5- The effect on afferent nerves

BoNT’s efficacy in conditions of detrusor overactivity may result not only from an inhibitory effect on detrusor muscle, but some effects of the drug may be mediated by altering afferent (sensory) input. (Hawthorn et al. 2000), recent basic and clinical evidence suggests that BoNT may have sensory inhibitory effects unrelated to its actions on acetylcholine release. (Khera et al. 2004). BoNT has also been shown to inhibit release of neuropeptides such as calcitonin generelated peptide, substances thought to play a role in overactive bladder conditions such as sensory urgency or chronic bladder inflammation (i.e., interstitial cystitis) (Rapp et al. 2006; Chuang et al. 2004).

6- Effects on Acetylcholine and ATP Release

ATP has also been implicated as a neurotransmitter in the generation of unstable contractions in idiopathic detrusor overactivity (Bayliss et al. 1999; O’Reilly et al. 2002). Studies on guinea pig (MacKenzie et al. 1982) and rat (Smith et al. 2003a) bladder strips have shown that BoNT is capable of inhibiting the release of both acetylcholine and ATP, providing a rationale for its possible use in treating patients with idiopathic overactive bladder. Bladder urothelium may play an important role in the sensory transduction mechanisms modulating micturition, particularly in conditions of increased sensory nerve transmission following chronic inflammation and spinal cord injury (Khera et al. 2004). Urothelial cells can release ATP (Birder et al. 2002), and the increased release of ATP from the urothelium of spinal cord injured rat
bladders could activate purine P2X3 receptors in epithelial and subepithelial layers to increase afferent nerve activity, accounting for the higher frequency of bladder contractions seen in both human and animal models of spinal cord injury.

BoNT was shown to inhibit ATP release from the urothelium but not the serosal side of the bladder, suggesting that BoNT treatment inhibits neurotransmitter release not only from efferent nerve endings but from sensory nerve terminals and/or urothelium as well (Khera et al. 2004). BoNT significantly impairs urothelial ATP release following spinal cord injury presents a plausible explanation for its clinical efficacy in the treatment of human neurogenic bladder dysfunction.

7- Effect on hot and cold sensitive sensory receptors

Originally described as a capsaicin receptor related to natural irritants (called vanilloids), the Transient Receptor Potential channel Vanilloid family member 1 (TRPV1) receptor is believed to function as an integrator of noxious stimuli, such as acids, heat, pollutants with a negative electronic charge, and endogenous pro-inflammatory substances. TRPV1 plays a key role in the perception of peripheral thermal and inflammatory pain (Morenilla-Palao et al. 2004). Recent findings indicate that BoNT blocks TRPV1 membrane translocation induced by protein kinase C, suggesting that activity-dependent delivery of channels to the neuronal surface may contribute to the buildup and maintenance of thermal inflammatory hyperalgesia in peripheral nociceptor terminals (Morenilla-Palao et al. 2004). Successful BoNT treatment for overactive bladder is associated with a significant decrease of TRPV1 and/or P2X3 in suburothelial nerve fibers (Apostolidis et al. 2005).
8- Effects on calcitonin gene-related peptide and substance P release

Sensory axons in the bladder contain both calcitonin gene-related peptide (CGRP) and substance P. These neuropeptides, which are released from nociceptive sensory endings in response to noxious stimuli, function as inflammatory response mediators (Basbaum and Jessell 2000).

Substance P acts on mast cells to produce degranulation, resulting in release of histamine and cytokines, which directly sensitize or excite nociceptors. In addition, both substance P and CGRP produce edema (substance P through plasma extravasation, and CGRP through dilation of peripheral blood vessels), causing liberation of bradykinin, all of which can lead to further activation of primary afferent fibers (Basbaum and Jessell 2000). Together with bradykinin and prostaglandins, substance P and CGRP also cause migration of leukocytes to the site of injury and clotting responses (Aoki 2005; Zubrzycka and Janecka 2000). BoNT has been shown in several preclinical models to block the release of CGRP, substance P, and glutamate from afferent nerve terminals (Aoki 2005; Chuang et al. 2004).

The effect of BoNT on sensory pathways is supported by results reported in preclinical models of bladder pain, in which intravesical application of BoNT significantly reduced pain responses and inhibited CGRP release from afferent nerve terminals, suggesting that BoNT may have clinical applications for the treatment of disorders such as interstitial cystitis and sensory urgency (Chuang et al. 2004; Rapp et al. 2006).

9- Inhibition of nerve growth factor release and receptor transport
In both animals and humans, the bladder increases production of nerve growth factor (NGF) in response to conditions such as spinal cord injury, denervation, inflammation, distension, or hypertrophy (Steers and Tuttle 2006).

It is produced in the smooth muscle of the urinary tract and urothelium of the bladder, and elevated NGF levels have been reported to trigger bladder overactivity, such as that seen in men with benign prostatic hyperplasia, women with interstitial cystitis, and in patients with idiopathic overactive bladder. Intravesical BoNT injection reduces nerve growth factor content in the bladder tissue of patients with neurogenic detrusor overactivity but it is unknown whether reduced bladder NGF results from decreased production, decreased uptake or a combination of both (Steers and Tuttle 2006).

The result of this action of BoNT is to decrease the hyperexcitability of C-fiber bladder afferents, thereby reducing neurogenic detrusor overactivity (Giannantoni et al. 2006).

**Histological changes after intra vesical injection**

Haferkamp et al. (2004) evaluated ultrastructural changes in overactive human detrusor tissue following BoNT injection in 30 biopsies from 24 patients with a diagnosis of neurogenic overactive bladder. Biopsies were taken before and 3 months after BoNT injection and during the wearing-off phase of the toxin’s efficacy. They observed no significant changes in muscle cell fascicles, intercellular collagen content or muscle cell degeneration when comparing biopsies taken before and after BoNT administration, although these results cannot be extrapolated to the possible structural effects of repeat injections. Unlike striated muscle, axonal sprouting in detrusor smooth muscle was limited.
following BoNT administration, and further research is required to determine if prolonged toxin dosing will elicit such a response. The results of an immunohistochemical study also suggested no significant axonal sprouting in the suburothelium of successfully treated patients (Apostolidis et al. 2005).

An important study reported histopathological changes in excised human neurogenic overactive bladders that could be associated with intradetrusor BoNT injections. Full-thickness specimens from bladders previously treated with one or more injections of BoNT showed significantly less fibrosis, but no differences in inflammation and edema compared to untreated ones; degrees of inflammation, edema and fibrosis were comparable in the two groups. Treated bladders had been injected with a mean number of 1.5 ± 0.8 injections, and the mean time between the last injection and surgery was 6.8 ± 2.8 months (Comperat et al. 2006).

Although the majority of long-term results are positive, more data is needed from both smooth and striated muscle. A case study by Coletti Moja and colleagues has described acute neuromuscular failure in a patient who had a 2-year history of regular abobotulinumtoxinA treatment (800–1,000 U every 3 months for limb spasticity) (Coletti Moja et al. 2004).

Biopsy investigations showed subacute denervation and inflammation of the deltoid muscle with unspecified diffuse abnormalities of group II afferent fibers at a site distal to the area of drug administration, with clinical features resembling an acute myasthenic-like syndrome. Such findings indicate that there is still much to learn about the effects of long-term exposure to BoNT. (Coletti Moja et al. 2004).
BoNT Antibody Production

Questions remain about the long-term use of BoNT and the potential for development of resistance, with repeated treatments often leading to a progressive decline in therapeutic response. It has been suggested that this decline may be caused by development of neutralizing antibodies to BoNT. The functionally relevant antigenicity of a BoNT preparation depends upon the amount of botulinum toxin presented to the immune system, which is in turn determined by the specific biological activity and the relationship between the biological activity and the amount of botulinum neurotoxin contained in the preparation (Dressler and Hallett 2006).

It is important to remember that almost all of the published papers on the presence of antibodies have been based on use of the original onabotulinumtoxinA (Botox) formulation. The current formulation has a much lower protein load and a reduced incidence of antibody production. is a clinical possibility, it is not a significant concern when considering the appropriate and safe use of the currently available formulations (with the possible exception of patients who may have had extended exposure to the original onabotulinumtoxinA formulation). It is important to note that if a patient does not respond to a particular injection, this does not necessarily indicate that the patient has developed blocking antibodies. In fact, the same patient may respond at a subsequent visit to exactly the same dose injected in the same muscles. (Chancellor and Smith, 2011).
Intravesical botulinum type-A toxin in the treatment of idiopathic detrusor overactivity

Common pharmacologic treatments to reduce bladder contractility include anticholinergics, antispasmodics, and tricyclic antidepressants. However, these therapies are associated with a high incidence of side effects including dry mouth, constipation and blurred vision, and often are not effective enough to reduce incontinence in cases of severe overactivity. Newer agents that target sensory fibers (e.g., capsaicin and resiniferatoxin) have shown early clinical promise although larger studies are still needed to judge the overall efficacy of this approach (Chancellor and de Groat 1999).

So, the only options available to patients who do not respond to or discontinue anticholinergic therapy are invasive procedures such as implantable devices to chronically stimulate the sacral nerve or surgical bladder augmentation. While these procedures may be effective for some patients, they are highly invasive, do not necessarily guarantee continence, and may have long term complications (Bosch 1998; Hohenfellner et al. 2000; Van Kerrebroeck et al. 1997).

Many studies have been carried out using botulinum neurotoxin (BoNT) in the treatment of patients who suffer from bladder overactivity. Suppression of involuntary detrusor contractions has been attempted via
the local administration of BoNT serotype A to the detrusor muscle, which inhibits acetylcholine release by cleaving SNAP 25, a protein integral to successful docking and release of vesicles within the nerve endings, including acetylcholine, calcitonin gene-related peptides (CGRP), glutamate and substance-P (Blasi et al. 1993; Cui et al. 2004; Meunier et al. 1996; Welch et al. 2000).

BoNT is believed to inhibit the acetylcholine-mediated detrusor contractions and may also inhibit other vesical-bound neurotransmitters in both the afferent and efferent pathways of the bladder wall, urothelium, or lamina propria (Chancellor et al. 2008).

**Technique of injection**

It should be emphasized that no standardized injection technique exists for BoNT injection in lower urinary tract tissues. For patients with idiopathic detrusor overactivity and OAB, onabotulinumtoxinA doses have ranged from 100 to 300 units. However, few controlled studies have been performed to determine the optimum dose or toxin dilution in idiopathic detrusor overactivity patient populations. Different injection paradigms have been described (i.e., trigone vs. trigone-sparing) although none has been proven to be superior to the other. In addition, fear of inducing vesicoureteral reflux with trigonal injection was disproven in a study by Karsenty and colleagues (Karsenty et al. 2007).

Bladder injections with BoNT can be made using either a rigid or flexible cystoscope, under general or local anesthesia.

The number of injections and volume of each injection given also vary widely. Such variability may affect the diffusion characteristics and efficacy of the treatment as well as the possibility of adverse events. Karsenty and associates prospectively randomized 24 neurogenic
patients to 300 U Botox over either 30 or 10 sites (Karsenty G, et al 2005).

They found no change in efficacy, safety, or QoL by a decrease in injection sites (increase in single-site bolus dose). This provides indirect evidence that a dose-dependent diffusion of BoNT-A activity occurs. This may allow the potential for using even fewer injection sites in the future, to further shorten and simplify the procedure. Controversy remains regarding the safety and usefulness of injecting the trigone. The concern is that injection near the ureteric orifices may lead to increased VUR, particularly in susceptible patients with NDO. Additionally the trigone has a rich submucosal sensory nerve plexus containing adrenergic, cholinergic, and nonadrenergic noncholinergic fibres. Injection here is postulated to therefore increase pain at the time of injection in awake patients, and the response to the neurotransmitter blockade by BoNT is unpredictable in such a complex plexus (Reitz, et al 2004). Conversely, the antinociceptive properties of BoNT may mean that the trigone is an ideal/important site for injection and there may be an argument to include the trigone in the injections (Harper, et al 2003).

Indeed Zermann et al, injected the trigone and bladder base in patients with severe urgency and frequency. No complications were reported and 57% of patients showed some improvement in frequency and bladder capacity due to the increased understanding of the role of the urothelium in overactive bladder (OAB) (Zermann et al, 2001).

Kuo et al. assessed suburothelial injections of BoNT. It was found that although this method of administration was more effective than detrusor injections, there was impaired bladder sensation and voiding efficiency.

Voiding difficulty was reported by 75% of patients and 30% required catheterisation. This suggests that blockade of detrusor
contractility through suburothelial sensory fibres was much more pronounced than at neuromuscular junctions or that only a small amount of diffusion of BoNT from the detrusor to the suburothelium occurs following detrusor injection, leading to the level of responses previously reported. (Kuo, et al., 2005).

**Trials on Botulium Toxin type A injection**

Sahai and colleagues detailed the first randomized placebo-controlled trial comparing the effect of 200 U of onabotulinumtoxinA versus saline bladder injection in 34 patients (i.e., 16 onabotulinumtoxinA and 18 placebo) with idiopathic detrusor overactivity and inadequately treated with 6 months of anticholinergic therapy (Sahai et al. 2007).

A total of 200 U of onabotulinumtoxinA was diluted in 20 ml of saline (i.e., 10 U/ml; or saline was used alone as placebo) and was injected in 20 places within the bladder wall, sparing the trigone. The primary endpoint measure was change in maximum cystometric capacity. OnabotulinumtoxinA improved maximum cystometric capacity significantly by 96 ml at 12 weeks. In addition, marked reductions in urinary frequency, and decreases in the number of urge urinary incontinence episodes and in the level of urgency was observed. The investigators also noted improvements in quality of life questionnaires in the onabotulinumtoxinA treated group.

Brubaker and associates compared the effects of 200 U of onabotulinumtoxinA versus saline bladder injections in 43 female patients with refractory urge urinary incontinence defined as >6 incontinence episodes/3 days and having failed at least two anticholinergic drugs (Brubaker et al. 2008). Patients were randomized in a 2:1 ratio: 28 patients received 200 U of onabotulinumtoxinA diluted in 6 ml of preservative free saline (i.e., 33 U/ml) and 15 patients received
saline injections alone. A total of 15–20 injections were placed in the posterior wall of the bladder sparing the trigone. The primary endpoint was time to failure, defined as a patient global impression of improvement score of 4 or greater 2 months after treatment. Sixty percent of patients treated with onabotulinumtoxinA demonstrated improvements in patient global impression of improvement score with a median duration of response of 373 days compared to 62 days or less for the placebo group. In addition, patients treated with onabotulinumtoxinA displayed greater than a 75% reduction in urge incontinence episodes by 3 day voiding diary. Unfortunately, the study was curtailed after recruiting 43 patients because 43% of patients treated with onabotulinumtoxinA required intermittent catheterization for a median duration of approximately 2 months.

Flynn and colleague evaluated the effect of two doses of onabotulinumtoxinA (i.e., 200 U and 300 U) versus placebo in 22 patients with refractory OAB defined as: greater than 2 daily urge incontinence episodes/day on a 3 day voiding diary, a 24 h pad weight of >100 g, and failure to respond to at least one anticholinergic medication (Flynn et al. 2009).

Candidates did not require urodynamically proven overactivity to be included in this study. The investigators were blinded to the dose of toxin given at the time of the study, thus the onabotulinumtoxinA results represent the combined results of both doses (i.e., 15 patients treated with onabotulinumtoxinA and 7 patients treated with placebo). The primary endpoints analyzed were the number of incontinence episodes/24 h and the quality of life and urinary distress questionnaire results. Interestingly, as opposed to the two prior studies, these investigators diluted onabotulinumtoxinA in only 3 ml (i.e., 66–100 U/ml) and injected the
bladder in 10–12 sites along the posterior bladder wall, sparing the trigone. At 6 weeks of follow-up, significant reductions in incontinence episodes/day were noted in the onabotulinumtoxinA treated group (i.e., 57.5%). In addition, marked improvements in quality of life and urinary distress symptoms scores were observed as well. Furthermore, pad weight decreased by 45% and the mean number of pads/day dropped from 4.4 to 2.2 pads/day. The largest and most recent randomized placebo-controlled study evaluated several doses of onabotulinumtoxinA (i.e., 50, 100, 150, 200, and 300 U) versus placebo in 313 patients with idiopathic OAB and urinary urge incontinence not adequately managed with anticholinergic medications (Dmochowski et al. 2010).

Patients had to experience at least eight urinary urge incontinence episodes/week and eight or more micturitions/day to be included in the study. The primary endpoint was weekly urinary urgency incontinence episodes at 12 weeks. Subjects were injected at 20 sites into the detrusor muscle (i.e., 0.5 ml/site) avoiding the trigone and the dome. The authors stated that significant difference from placebo was observed in the number of urgency incontinence episodes/week at many time points. However, they also stated that a clear dose response effect was not observed in regards to efficacy, although by non-parametric analysis minimal additional benefit was achieved by doses above 150 U of onabotulinumtoxinA. In contrast, a clear dose response relationship was displayed in the proportion of patients with a posttreatment residual urine volume of 200 ml or greater.

Anger and colleagues performed a meta-analysis of the three randomized, placebo controlled trials up to that time point using onabotulinumtoxinA in patients with idiopathic OAB (Anger et al. 2010). Pooled analysis of the three studies revealed that patients treated with onabotulinumtoxinA had almost four fewer episodes of urge urinary
incontinence per day than placebo treated patients. Their analysis also revealed that onabotulinumtoxinA treated patient’s demonstrated improved quality of life scores, estimated by a 15 point drop in urinary distress inventory (UDI-6) scores compared to placebo injected patients. However, the benefit from onabotulinumtoxinA was curbed by the nearly ninefold increase in the risk of elevated post-void residual urine volume in onabotulinumtoxinA treated patients compared to controls. A recent European expert panel report gave BoNT the highest grade level recommendation (i.e., grade A) for the treatment of refractory idiopathic detrusor overactivity (Apostolidis et al. 2009).
**Side effects:**

Many studies demonstrated significant dose-dependent improvements in urinary symptoms and urodynamic parameters in patients with OAB (Sahai et al, 2007, Kuo et al, 2007 – Dmochowski et al 2009). However, the incidence of adverse events is also associated with increasing dose of BoNTA (Kuo 2006, Dmochowski et al 2009).

The main adverse events associated with BoNTA injection are acute urinary retention (AUR), large postvoid residual (PVR), difficulty in urination, and urinary tract infection (UTI), which occurred in approximately 20–43% of patients (Kessler et al, 2005, Kuo 2006, Sahai et al, 2007, Brubaker et al, 2008).

Large PVR after BoNTA injection was clinically relevant and clean intermittent catheterization (CIC) was necessary (Kuo, 2005, Kuo, 2006, Brubaker et al, 2008). In a recent report, complete continence after 200 U Botox injection was 51% at 4wk (Khan et al, 2010).

Although patients without complete continence may experience improvement in urgency incontinence, they might not be satisfied with the treatment outcome due to these bothersome adverse effects. (Chancellor and Smith, 2011).

**Tachyphylaxis:**

Due to the antigenicity of BoNT, after repeat injections a small number of patients mount an immune response with the formation of neutralising antibodies. To minimise the small risk of BoNT resistance, most investigators currently recommend waiting at least 3 mo between
treatments, avoiding the use of booster injections and using the smallest dose that achieves the desired clinical effect (Maria et al, 2005). The newer formulation of Botox used after 1998 is thought to have drastically reduced the occurrence of resistance (Rackley et al, 2004).

There have been a couple of case reports of the development of resistance to BoNT-A with continued efficacy with therapy switch to BoNT-B (Reitz and Schurch, 2004, Pistolesi et al, 2004). The different target proteins for these toxins may explain the continued efficacy following the development of resistance to one serotype. However, the presence of some cross reactive antibodies may limit this use. (Chancellor and Smith, 2011).
Results

Our study included 80 patients complaining from OAB symptoms 63 females (78.8%) and 17 males (20.2%) with mean age 30.8±7.9. (Table 1-3 and fig. 12)

(Table 1) Description of the studied sample:

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (N=80)</th>
<th>% (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The studied groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botox 100</td>
<td>40</td>
<td>50.0</td>
</tr>
<tr>
<td>Botox 200</td>
<td>40</td>
<td>50.0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>17</td>
<td>21.2</td>
</tr>
<tr>
<td>female</td>
<td>63</td>
<td>78.8</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td>30.8±7.9</td>
<td>17</td>
<td>48</td>
</tr>
</tbody>
</table>

(Table 2) Comparing both groups regarding gender:

<table>
<thead>
<tr>
<th>Gender</th>
<th>Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Botox 100</td>
<td>Botox 200</td>
</tr>
<tr>
<td>male</td>
<td>Count</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>% within group</td>
<td>15.0%</td>
</tr>
<tr>
<td>female</td>
<td>Count</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>% within group</td>
<td>85.0%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>% within group</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

X² =1.87 P=0.17

(Table 3) Comparing both groups regarding age:

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>St. “t”</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bot Tox 100</td>
<td>30.22</td>
<td>8.37</td>
<td>0.63</td>
</tr>
<tr>
<td>Bot Tox 200</td>
<td>31.35</td>
<td>7.61</td>
<td>0.63</td>
</tr>
</tbody>
</table>
Baseline data of the studied sample (table 4)
A -Comparing both groups regarding symptoms (clinically)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100 (N=40)</th>
<th>Botox 200 (N=40)</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>1.60 ± 0.496</td>
<td>1.67 ± 0.525</td>
<td>0.66</td>
<td>0.51</td>
</tr>
<tr>
<td>Nocturia</td>
<td>0.87 ± 0.965</td>
<td>1.20 ± 1.202</td>
<td>1.33</td>
<td>0.19</td>
</tr>
<tr>
<td>Urgency</td>
<td>4.70 ± 0.464</td>
<td>4.67 ± 0.474</td>
<td>0.24</td>
<td>0.81</td>
</tr>
<tr>
<td>UUI</td>
<td>1.67 ± 1.899</td>
<td>1.80 ± 2.002</td>
<td>0.29</td>
<td>0.77</td>
</tr>
<tr>
<td>OABSS</td>
<td>8.85 ± 2.166</td>
<td>9.35 ± 1.994</td>
<td>1.07</td>
<td>0.28</td>
</tr>
</tbody>
</table>

(Table 4) Baseline data of the studied sample

Assessment of the studied sample after 1, 3, 6 and 9 monthes post treatment in comparison with the baseline clinical data (table 5-8):
A statistically no significant difference is observed when analyzing voiding frequency, urgency, nocturia and urge urinary incontinence (OABSS) post-treatment in both groups except in 9\textsuperscript{th} month follow up. P value was <0.001 , 0.017 , <0.001 , 0.003 and <0.001 as regrds to frequency, nocturia ,urgency and urge urinary incontinence correspondingly.

(Table 5) Comparing both groups regarding clinical symptoms 1 month post treatment.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100 (N=40)</th>
<th>Botox 200 (N=40)</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.45 ± 0.503</td>
<td>0.42 ± 0.500</td>
<td>0.22</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>0.23 ± 0.422</td>
<td>0.15 ± 0.361</td>
<td>0.85</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Nocturia</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.40 ± 1.37</td>
<td>1.9 ± 1.12</td>
<td>1.77</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>0.77 ± 1.073</td>
<td>0.85 ± 1.098</td>
<td>0.31</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>UUI</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.85 ± 2.537</td>
<td>3.32 ± 2.092</td>
<td>0.91</td>
<td>0.36</td>
</tr>
</tbody>
</table>

(Table 6) Comparing both groups regarding clinical symptoms 3 month post treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100 (N=39)</th>
<th>Botox 200 (N=40)</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.42 ± 0.500</td>
<td>0.33 ± 0.474</td>
<td>0.92</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>0.13 ± 0.334</td>
<td>0.13 ± 0.334</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Nocturia</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.07 ± 1.163</td>
<td>1.45 ± 1.31</td>
<td>0.15</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>0.65 ± 0.975</td>
<td>0.65 ± 0.948</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>UUI</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.23 ± 2.391</td>
<td>2.55 ± 2.417</td>
<td>0.61</td>
<td>0.54</td>
</tr>
</tbody>
</table>

(Table 7) Comparing both groups regarding clinical symptoms 6 month post treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100 (N=38)</th>
<th>Botox 200 (N=38)</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.51 ± 0.506</td>
<td>0.30 ± 0.464</td>
<td>1.94</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>0.13 ± 0.338</td>
<td>0.12 ± 0.334</td>
<td>0.042</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Nocturia</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.97 ± 1.135</td>
<td>1.25 ± 1.031</td>
<td>1.13</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>0.67 ± 0.982</td>
<td>0.72 ± 1.085</td>
<td>0.25</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>UUI</strong></td>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.28 ± 2.361</td>
<td>2.37 ± 2.518</td>
<td>0.17</td>
<td>0.86</td>
</tr>
</tbody>
</table>

(Table 8) Comparing both groups regarding clinical symptoms 9 month post treatment.
### Table 9 and Figure 13 demonstrates OABSS in both groups over the study time.

**Table 9** Studying the OABSS over the period of the study among both groups:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100</th>
<th></th>
<th>Botox 200</th>
<th></th>
<th>St. ‘t’</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.</td>
<td>Mean ± SD</td>
<td>n.</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OABSS pre</td>
<td>40</td>
<td>8.85 ± 2.166</td>
<td>40</td>
<td>9.35 ± 1.994</td>
<td>1.07</td>
<td>0.28</td>
</tr>
<tr>
<td>OABSS 1</td>
<td>40</td>
<td>2.85 ± 2.537</td>
<td>40</td>
<td>3.32 ± 2.092</td>
<td>0.91</td>
<td>0.36</td>
</tr>
<tr>
<td>OABSS 3</td>
<td>40</td>
<td>2.23 ± 2.391</td>
<td>40</td>
<td>2.55 ± 2.417</td>
<td>0.61</td>
<td>0.54</td>
</tr>
<tr>
<td>OABSS 6</td>
<td>39</td>
<td>2.28 ± 2.361</td>
<td>40</td>
<td>2.37 ± 2.518</td>
<td>0.17</td>
<td>0.86</td>
</tr>
<tr>
<td>OABSS 9</td>
<td>38</td>
<td>5.30 ± 2.110</td>
<td>38</td>
<td>2.60 ± 2.307</td>
<td>5.45</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

(Figure 13) The OABSS over the period of the study among both groups.

Collectively table 10 and 11 shows the assessment of symptoms (frequency of micturation, nocturia, urgency and urge urinary incontinence) and OABSS over the period of the study among group A and B correspondingly.

**Group A**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>1 month later</th>
<th>3 months later</th>
<th>6 months later</th>
<th>9 months later</th>
</tr>
</thead>
<tbody>
<tr>
<td>OABSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(Table 10)

* → significant in comparison to “before intervention”
† → significant in comparison to “1 month later”
‡ → significant in comparison to “3 months later”
∆ → significant in comparison to “6 months later”

(Paired “t” test was the test of significance)

(Group B)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before intervention</th>
<th>1 month later</th>
<th>3 months later</th>
<th>6 months later</th>
<th>9 months later</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Frequency</td>
<td>1.60 ± 0.496</td>
<td>0.45* ± 0.503</td>
<td>0.42* ± 0.500</td>
<td>0.51* ± 0.506</td>
<td>1.10*±‡∆</td>
</tr>
<tr>
<td>Nocturia</td>
<td>0.87 ± 0.965</td>
<td>0.23* ± 0.422</td>
<td>0.13* ± 0.334</td>
<td>0.13* ± 0.338</td>
<td>0.36* ± 0.488</td>
</tr>
<tr>
<td>Urgency</td>
<td>4.70 ± 0.464</td>
<td>1.40* ± 1.37</td>
<td>1.07* ± 1.163</td>
<td>0.97*± 1.135</td>
<td>2.57*±‡∆</td>
</tr>
<tr>
<td>UUI</td>
<td>1.67 ± 1.899</td>
<td>0.77* ± 1.073</td>
<td>0.65* ± 0.975</td>
<td>0.67* ± 0.982</td>
<td>1.26*±‡∆</td>
</tr>
<tr>
<td>OABSS</td>
<td>8.85 ± 2.166</td>
<td>2.85* ± 2.537</td>
<td>2.23*± 2.391</td>
<td>2.28*± 2.361</td>
<td>5.30*±‡∆</td>
</tr>
</tbody>
</table>

(Table 11)

(B) - Comparing both groups regarding urodynamic findings

(Table 12) Comparing both groups regarding pre treatment urodynamic findings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100 (N=40)</th>
<th>Botox 200 (N=40)</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First desire</td>
<td>200.0 ± 35.73</td>
<td>199.0 ± 35.71</td>
<td>0.13</td>
<td>0.9</td>
</tr>
<tr>
<td>Strong desire</td>
<td>259.0 ± 64.40</td>
<td>260.5 ± 63.08</td>
<td>0.11</td>
<td>0.91</td>
</tr>
<tr>
<td>Detrusor pressure</td>
<td>27.8 ± 10.12</td>
<td>30.6 ± 11.09</td>
<td>1.15</td>
<td>0.25</td>
</tr>
<tr>
<td>MCC</td>
<td>277.7 ± 75.29</td>
<td>289.2 ± 70.83</td>
<td>0.7</td>
<td>0.48</td>
</tr>
</tbody>
</table>

(Table 12)
Assessment of the studied sample after 3, 6 and 9 months post treatment in comparison with the baseline urodynamic data (table 13-15):

A statistically no significant difference is observed when analyzing Frist and strong desire for micturation, Detrusor pressure and maximum cystometric capacity post treatment in both groups except in 9th month follow up. P value was <0.001 in all mentioned urodynamic items.

(Table 13) Comparing both groups regarding urodynamics 3 month post treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100 (N=40)</th>
<th>Botox 200 (N=40)</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First desire</td>
<td>318.0 59.62</td>
<td>300.2 44.28</td>
<td>1.51</td>
<td>0.13</td>
</tr>
<tr>
<td>Strong desire</td>
<td>427.5 58.78</td>
<td>407.2 41.44</td>
<td>1.78</td>
<td>0.08</td>
</tr>
<tr>
<td>Detrusor pressure</td>
<td>11.1250 6.31720</td>
<td>9.2500 3.01917</td>
<td>1.69</td>
<td>0.09</td>
</tr>
<tr>
<td>MCC</td>
<td>439.0 55.22</td>
<td>439.0 41.24</td>
<td>0.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

(Table 14) Comparing both groups regarding urodynamics 6 month post treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100 (N=39)</th>
<th>Botox 200 (N=40)</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First desire</td>
<td>309.2 58.14</td>
<td>295.5 40.86</td>
<td>1.21</td>
<td>0.22</td>
</tr>
<tr>
<td>Strong desire</td>
<td>417.9 51.20</td>
<td>401.2 38.35</td>
<td>1.64</td>
<td>0.1</td>
</tr>
<tr>
<td>Detrusor pressure</td>
<td>10.6 5.36</td>
<td>9.07 3.22</td>
<td>1.55</td>
<td>0.12</td>
</tr>
<tr>
<td>MCC</td>
<td>437.4 55.36</td>
<td>438.2 40.99</td>
<td>0.07</td>
<td>0.94</td>
</tr>
</tbody>
</table>

(Table 15) Comparing both groups regarding urodynamics 9 month post treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100 (N=38)</th>
<th>Botox 200 (N=38)</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First desire</td>
<td>246.8 53.78</td>
<td>291.8 42.82</td>
<td>4.03</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Strong desire</td>
<td>313.1 67.38</td>
<td>392.1 37.28</td>
<td>6.32</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Detrusor pressure</td>
<td>19.2 7.78</td>
<td>10.4 3.97</td>
<td>6.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MCC</td>
<td>350.0 69.08</td>
<td>430.5 34.24</td>
<td>6.44</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>
Tables 16-18 and figures 14-17 shows the urodynamic items changes all over the study time.

(Table 16) and (Figure 14)  Studying the first desire over the period of the study among both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100</th>
<th>Botox 200</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.</td>
<td>Mean ± SD</td>
<td>n.</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>First desire pretreatment</td>
<td>40</td>
<td>200.0 35.73</td>
<td>40</td>
<td>199.0 35.71</td>
</tr>
<tr>
<td>First desire 3</td>
<td>40</td>
<td>318.0 59.62</td>
<td>40</td>
<td>300.2 44.28</td>
</tr>
<tr>
<td>First desire 6</td>
<td>39</td>
<td>309.2 58.14</td>
<td>40</td>
<td>295.5 40.86</td>
</tr>
<tr>
<td>First desire 9</td>
<td>38</td>
<td>246.8 53.78</td>
<td>38</td>
<td>291.8 42.82</td>
</tr>
</tbody>
</table>

(Figure 14)

(Table 17) and (Figure 15)  Studying the strong desire over the period of the study among both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100</th>
<th>Botox 200</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.</td>
<td>Mean ± SD</td>
<td>n.</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Strong desire pretreatment</td>
<td>40</td>
<td>259.0 64.40</td>
<td>40</td>
<td>260.5 63.08</td>
</tr>
<tr>
<td>Strong desire 3</td>
<td>40</td>
<td>427.5 58.78</td>
<td>40</td>
<td>407.2 41.44</td>
</tr>
<tr>
<td>Strong desire 6</td>
<td>39</td>
<td>417.9 51.20</td>
<td>40</td>
<td>401.2 38.35</td>
</tr>
<tr>
<td>Strong desire 9</td>
<td>38</td>
<td>313.1 67.38</td>
<td>38</td>
<td>392.1 37.28</td>
</tr>
</tbody>
</table>

(Table 17)
(Table 18) and (Figure 16) Studying the detrusor pressure over the period of the study among both groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100</th>
<th>Botox 200</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.</td>
<td>Mean ± SD</td>
<td>n.</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Detrusor pressure pretreatment</td>
<td>40</td>
<td>27.8 ± 10.12</td>
<td>40</td>
<td>30.6 ± 11.09</td>
</tr>
<tr>
<td>Detrusor pressure 3</td>
<td>40</td>
<td>11.1 ± 6.317</td>
<td>40</td>
<td>9.2 ± 3.01</td>
</tr>
<tr>
<td>Detrusor pressure 6</td>
<td>39</td>
<td>10.6 ± 5.36</td>
<td>40</td>
<td>9.07 ± 3.22</td>
</tr>
<tr>
<td>Detrusor pressure 9</td>
<td>38</td>
<td>19.2 ± 7.78</td>
<td>38</td>
<td>10.42 ± 3.97</td>
</tr>
</tbody>
</table>
(Table 19) and (Figure 17) Studying the MCC over the period of the study among both groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100</th>
<th></th>
<th></th>
<th>Botox 200</th>
<th></th>
<th></th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.</td>
<td>Mean</td>
<td>± SD</td>
<td>n.</td>
<td>Mean</td>
<td>± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCC pretreatment</td>
<td>40</td>
<td>277.7</td>
<td>75.29</td>
<td>40</td>
<td>289.2</td>
<td>70.83</td>
<td>0.7</td>
<td>0.48</td>
</tr>
<tr>
<td>MCC3</td>
<td>40</td>
<td>439.0</td>
<td>55.22</td>
<td>40</td>
<td>439.0</td>
<td>41.24</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>MCC6</td>
<td>39</td>
<td>437.4</td>
<td>55.36</td>
<td>40</td>
<td>438.2</td>
<td>40.99</td>
<td>0.07</td>
<td>0.94</td>
</tr>
<tr>
<td>MCC9</td>
<td>38</td>
<td>350.0</td>
<td>69.08</td>
<td>38</td>
<td>430.5</td>
<td>34.24</td>
<td>6.44</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Lastly, in our work by using EQ-5D questionnaire, it was noted that there is improvement in the quality of life in comparison to the pretreatment score and there is no significant difference between the
study groups except at the 9th month follow up. Group B maintained the high score in comparison to Group A (P value <0.001). (Table 20 and figure 18)

(Table 20) Studying the total QOL score over the period of the study among both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100</th>
<th>Botox 200</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.</td>
<td>Mean ± SD</td>
<td>n.</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>QOL pretreatment</td>
<td>40</td>
<td>42.7 ± 8.58</td>
<td>40</td>
<td>40.8 ± 6.82</td>
</tr>
<tr>
<td>QOL 1</td>
<td>40</td>
<td>83.6 ± 7.54</td>
<td>40</td>
<td>82.8 ± 7.60</td>
</tr>
<tr>
<td>QOL 3</td>
<td>40</td>
<td>72.4 ± 16.45</td>
<td>40</td>
<td>77.3 ± 11.67</td>
</tr>
<tr>
<td>QOL 6</td>
<td>39</td>
<td>73.4 ± 12.21</td>
<td>40</td>
<td>77.3 ± 10.12</td>
</tr>
<tr>
<td>QOL 9</td>
<td>38</td>
<td>68.5 ± 7.57</td>
<td>38</td>
<td>77.1 ± 10.00</td>
</tr>
</tbody>
</table>

Collectively table 21 and 22 shows the assessment of, urodynamic findings and QOL over the period of the study among group A and B correspondingly.

(Group A)
**Table 21**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before intervention</th>
<th>1 month later</th>
<th>3 months later</th>
<th>6 months later</th>
<th>9 months later</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>First desire</td>
<td>200.0 ± 35.73</td>
<td>318.0* ± 59.62</td>
<td>309.2* ± 58.14</td>
<td>246.8*‡Δ ± 53.78</td>
<td></td>
</tr>
<tr>
<td>Strong desire</td>
<td>259.0 ± 64.40</td>
<td>427.5* ± 58.78</td>
<td>417.9* ± 51.20</td>
<td>313.1*‡Δ ± 67.38</td>
<td></td>
</tr>
<tr>
<td>Detrusor pressure</td>
<td>27.8 ± 10.12</td>
<td>11.1* ± 6.317</td>
<td>10.6* ± 5.36</td>
<td>19.2*‡Δ ± 7.78</td>
<td></td>
</tr>
<tr>
<td>MCC</td>
<td>277.7 ± 75.29</td>
<td>439.0* ± 55.22</td>
<td>437.4* ± 55.36</td>
<td>350.0*‡Δ ± 69.08</td>
<td></td>
</tr>
<tr>
<td>QOL</td>
<td>42.7 ± 8.58</td>
<td>83.6* ± 7.54</td>
<td>72.4*‡ ± 16.45</td>
<td>73.4*‡ ± 12.21</td>
<td>68.5*‡Δ ± 7.57</td>
</tr>
</tbody>
</table>

*→ significant in comparison to “before intervention”
† → significant in comparison to “1 month later”
‡→ significant in comparison to “3 months later”
Δ→ significant in comparison to “6 months later”

(Paired “t” test was the test of significance)

**Group B**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before intervention</th>
<th>1 month later</th>
<th>3 months later</th>
<th>6 months later</th>
<th>9 months later</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>First desire</td>
<td>199.0 ± 35.71</td>
<td>300.2* ± 44.28</td>
<td>295.5* ± 40.86</td>
<td>291.8*‡ ± 42.82</td>
<td></td>
</tr>
<tr>
<td>Strong desire</td>
<td>260.5 ± 63.08</td>
<td>407.2* ± 41.44</td>
<td>401.2* ± 38.35</td>
<td>392.1*‡ ± 37.28</td>
<td></td>
</tr>
<tr>
<td>Detrusor pressure</td>
<td>30.6 ± 11.09</td>
<td>9.2* ± 3.01</td>
<td>9.07* ± 3.22</td>
<td>10.42* ± 3.97</td>
<td></td>
</tr>
<tr>
<td>MCC</td>
<td>289.2 ± 70.83</td>
<td>439.0* ± 41.24</td>
<td>438.2* ± 40.99</td>
<td>430.5* ± 34.24</td>
<td></td>
</tr>
<tr>
<td>QOL</td>
<td>40.8 ± 6.82</td>
<td>82.8* ± 7.60</td>
<td>77.3*‡ ± 11.67</td>
<td>77.3*‡ ± 10.12</td>
<td>77.1*‡ ± 10.00</td>
</tr>
</tbody>
</table>

**Table 22**

*There is three recorded adverse events,* Early postoperative hematuria was observed 24 patients (63.2%) in group I in and 26 patients (68.4%) in group II also during follow up dysuria was observed in 3 and 12 patients in group I and II respectively. UTI was detected in 3 and 7 patients in group A and B respectively. Non significant increase in PVU was reported and was dose dependent.

**Table 23 and 24 show a comparison between the study groups as regards to dysuria and heamaturia**

**Table 23** Comparing the studied groups regarding heamaturia
<table>
<thead>
<tr>
<th>Heamaturia</th>
<th>Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Botox 100</td>
<td>Botox 200</td>
</tr>
<tr>
<td>no</td>
<td>Count</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>% within group</td>
<td>36.8%</td>
</tr>
<tr>
<td>yes</td>
<td>Count</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>% within group</td>
<td>63.2%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>% within group</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 0.23 \quad P = 0.63 \]

(Table 24) Comparing the studied groups regarding dysuria

<table>
<thead>
<tr>
<th>Dysuria</th>
<th>Group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Botox 100</td>
<td>Botox 200</td>
</tr>
<tr>
<td>no</td>
<td>Count</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>% within group</td>
<td>92.1%</td>
</tr>
<tr>
<td>yes</td>
<td>Count</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>% within group</td>
<td>7.9%</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>% within group</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 6.7 \quad P = 0.009^* \]

This figure (19) shows a comparison between the study groups as regards to dysuria
As regarding the post voiding residual urine, it was noted that PVU increased post treatment more than pre treatment but PVU had a higher levels in group B than group A and it decreased at the 9th month follow up in group A and here there was a significant difference as compared with group B (Table 23 and figure 20).

(Table 25) Studying the PVU over the period of the study among both groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Botox 100</th>
<th>Botox 200</th>
<th>St. 't'</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.</td>
<td>Mean ± SD</td>
<td>n.</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>PVR pretreatment</td>
<td>40</td>
<td>25.75 ± 12.83</td>
<td>40</td>
<td>27.40 ± 15.05</td>
</tr>
<tr>
<td>PVR3</td>
<td>40</td>
<td>40.00 ± 21.42</td>
<td>40</td>
<td>47.37 ± 11.87</td>
</tr>
<tr>
<td>PVR6</td>
<td>39</td>
<td>39.23 ± 12.48</td>
<td>40</td>
<td>42.00 ± 10.05</td>
</tr>
<tr>
<td>PVR9</td>
<td>38</td>
<td>24.21 ± 8.58</td>
<td>38</td>
<td>29.21 ± 11.30</td>
</tr>
</tbody>
</table>

(Figure 20)
Discussion

Overactive bladder is a common condition in adult population, with impact on physical, psychological and social well-being, and presents an important burden to the economy of health service (Correia et al, 2009).

Overactive bladder symptoms are frequent complaints of patients attending urology and gynecology clinics. In many patients, the cause for these symptoms is detrusor overactivity (DO) which in most cases is idiopathic with no obvious underlying neurological abnormality. Patients with DO suffer from sleep disturbance, psychological distress from embarrassment due to incontinence and disruption to social and work life that affects quality of life (Reeves et al, 2006).

Anticholinergic therapy is the first line treatment for overactive bladder but is limited by side effects or lack of therapeutic goal attainment. (MacDiarmid et al, 2010).

Sacral neuromodulation or surgical bladder augmentation were the available options for treatment of IOAB, however they are highly invasive and have long term complications. (Hohenfellner et al, 2000).

A European consensus group gave a grade A recommendation for BoNTA use in IDO (Apostolidis et al, 2009) and a recent systematic review suggested its use for refractory OAB is well justified. (Mangera et al, 2011).
In relation to the aforementioned results, our study showed a significant improvement in all clinical overactive bladder symptom score items (frequency, nocturia, urgency and UUI) after BoNTA treatment.

There was no significant difference between 100 U and 200 U at month 1, 3 and 6 post injection. The 200 U BoNTA dosage demonstrated consistent improvements till the end of the study and the significant difference between groups was at month 9 post injection. However there was significant amelioration at month 9 when compared to those at month 1, 3 and 6 in patients were received 100 U except for nocturia.

The response rate and the incidence of side effects of BoNTA on IOAB are closely related to the dose. (Sahai et al, 2009).

A dose-related effect was observed in urodynamic measures and safety outcomes and QoL. The optimal dosing of BoNTA still remains to be defined (Apostolidis et al, 2009).

Dmochowski and his associates, in a dose-ranging trial comparing 50, 100, 150, 200, and 300 U onabotulinumtoxinA in patients with IDO, showed that 100 U may be the optimum dose that appropriately balances the benefits with adverse events (Dmochowski et al, 2010).

Many studies reduced the dose of BoNTA to 100 U and a satisfactory outcome can still be achieved for IDO due to the high incidence of side effects after BoNTA injections (Chapple et al, 2013-Mangera et al, 2011 -Cohen et al, 2009 –Kuo, 2009 and Jeffery, 2007).

Sahai A and his colleagues confirm that detrusor injections of 200 U yields along response duration of 12-15 months. (Sahai A et al, 2009).
Brubaker and his associates reported a mean duration of efficacy of 370 days of BoNTA 200u (Brubaker et al, 2008).

Regarding the changes in the urodynamic parameters after BoNTA injection, we found that the bladder capacity returned gradually, however the maximum effect on significant increase in cystometric capacity was observed at month three after treatment in both groups in our study. Although BoNTA remained therapeutically effective up to 6 months, the effect reduced significantly in group A with time to the end of the study.

Doses ranging from 50 U to 300 U, showed significantly greater improvement in symptoms of frequency, urgency, and UI as well as in urodynamic measures in the active-treatment arms with BoNTA doses of at least 100 U. (Dmochowski et al, 2010 - Brubaker et al, 2008 - Sahai et al, 2007)

Regarding the optimal BoNTA dose, one study suggested minimal added benefit above 150 U, (Dmochowski et al, 2010) and a Class III study comparing 100 U vs. 150 U failed to demonstrate any differences between the two doses. (Cohen et al, 2009).


Using the King’s Health Questionnaire, Dmochowski et al. observed an improved QoL with 100 U and 150 U BoNTA injections at month 6, whereas no improvement could be observed with a 50 U dose. (Dmochowski et al, 2010).
Using a VAS, Cohen and his colleagues observed no difference between 100 U and 150 U at month 3 (Cohen et al, 2009).

In our study using EQ-5D quality of life questionnaire (Kind, 2003), QoL improvements were maintained for up to 6 months with clinical and urodynamic improvements in both groups and this improvement was prolonged till 9 months post injection in group B.

The number of adverse events was lower than observed by others. In this study there was no patient has developed urinary retention or significant elevation of post-void residual urine (PVR >100 ml) following injection.

Many studies of BoNTA for IDO reported a 24–43% incidence of transient urinary retention requiring CIC and also reported a 32–72% incidence of a large PVR and difficulty in urination. (Kessler et al, 2009-Khan et al, 2009- Kuo, 2006- Kessler et al, 2005- Popat et al, 2005).

Although a large PVR and urinary retention remain obstacles for the wide use of BoNTA in treatment of refractory DO, no factors predicting these adverse effects have been found. (Kuo HC, 2009).

Bauer and his associates have specifically looked at adverse events after injection of 100 U, 200 U and 500 U of BoNTA by using a patient questionnaire, however he concluded the higher doses of the toxin led to higher rates of adverse events. (Bauer et al, 2011).
It was observed gross mild hematuria which was procedural related and resolved conservatively. In the series by Sahai and his associates. (Sahai et al, 2007) the hematuria was up to 7.8% and 3.6% by Chapple and his colleagues. (Chapple et al, 2013).

Dysuria was increased in group II in this study while others reported in patients received 100U 5.8% (Chapple et al, 2013), 4% (Werner et al, 2005) whereas, it was more for 200 U 33%. (Kuo HC, 2004).


This study revealed more cases had UTI in group B; all cases received proper antibiotics and analgesics, which was comparable with others in which the rate of UTI ranged from 13% to 44% (Chapple et al, 2013- Kuo et al, 2010- Cohen et al, 2009- Flynn et al, 2009 –Brubaker et al, 2008, Sahai et al, 2007).
Discussion

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الملخص العربي

المثانة المتهيجة عبارة عن مجموعة من أعراض أسفل الجهاز البولي تشمل عجلة في التبول مع أو بدون سلس بولي لا ارادي ويصبح زيادة عدد مرات التبول ، وبلغ نسبة مرضى المثانة المتهيجة في البلاد العربية ما يقارب 17% من مرضى المسالك البولية ولاحظ زيادة نسبة الإصابة بالمرض بين السيدات متوسطى العمر و يؤثر مرض المثانة المتهيجة تأثيرا كبيرا على نمط حياة المرضى .

وهناك العديد من طرق العلاج لهذا المرض فمنها العلاج الطبي الذي يعد حجر الأساس والأكثر استخداما في علاج هذا المرض وكذلك العلاج الجراحي والذي يندر استخدامه كإحدى طرق العلاج لإحتمال حدوث الكثير من الضعفات والأثار الجانبية .

ويعد حقن عقار (سم البوتولنيوم) في عضلة المثانة البولية من أهم الطرق الحديثة والفعالة لعلاج المثانة المتهيجة وخاصة في الحالات المستعصية للعلاج الطبي أو المرضى الذين لا يستطيعون احتمال الأثار الجانبية للعلاج أو لديهم مواني لاستخدامه .

كما يعتبر هذا العقار طريقة سريعة للتدخل العلاجي في هذا المرض وتحري عليه العديد من البحوث وما زال يخضع للتحقيق وقد أثبت نجاحا كبيرا إلا أن له بعض الأثار الجانبية .

أما بالنسبة لتحديد الجرعة العلاجية لهذا العقار فلم يتم تحديدها بعد ،

ألا أن بعض الأبحاث مؤخرا تم اجراها لتحديد الجرعة المثلى التي تعني أقل جرعة للعقار تحقق أعلى كفاءة للعلاج حتى يتم تجنب الآثار الجانبية له .

ولذلك كان الهدف من هذه الدراسة مقارنة فعالية هذا العقار بجرعته المعتادة وهي 200 وحدة واستخدامه بجرعة مخفضة وهي 100 وحدة و تم
إجراء هذه الدراسة على 80 مريض ممن يحضرون إلى مستشفى بنها الجامعي طلبا للعلاج بقسم المسالك البولية والذين يعانون من مرض المثانة العصبي المستعصية للعلاج الطبي.

وتم تقسيمهم عشوائيا إلى مجموعتين كل مجموعة تتضمن 40 مريضا:
في المجموعة الأولى تم حقن عضلة المثانة ب 200 وحدة من العقار.
وفي المجموعة الثانية تم حقن عضلة المثانة ب 100 وحدة من العقار.

وقد خضع جميع المرضى قبل الدراسة للفحوصات والتحليل اللازمة مثل (التاريخ المرضي، الفحص الطبي الكامل، التحاليل الطبية الكاملة، مثل تحليل البول وعمل مزروعة بول إذا تطلب الأمر، وكذلك التحاليل الروتينية ما قبل العملية كتحليل وظائف الكلى و الكبد وصورة الدم الكاملة) وذلك تم عمل أشعة تلقيزونية على البطن والحوض لجميع المرضى وكذلك الأشعات المطلوبة إذا اقتضت حالة المريض، أيضا تم عمل فحص ديناميكية التبول للمرضى الخاصين للدراسة.

وتم متابعة المرضى بعد حفن العقار بعد 1، 3، 6، 9 أشهر أكلينيكيًا.

وبعد رصد النتائج وتحليلها احصائيا لوحظ وجود تحسن واضح لكلا المجموعتين من حيث الأعراض الأكلينيكية وعناصر ديناميكية التبول وجودة حياة المرضى متضمنة بعد العلاج وأيضا تم عمل فحص ديناميكية التبول للمريض بعد 3، 6، 9 أشهر.

وانتهى من خلال هذه التجربة أن وجود نفس المركب في المجموعة الثانية فقط في الشهر التاسع في المتابعة بعد الحقن.
أما بالنسبة للآثار الجانبية فقد تم رصدها بنسبة أكبر في المجموعة الثانية بمعنى أنه بزيادة الجرعة تزداد الآثار الجانبية. وقد لوحظ تواجد ما توصلت إليه هذه الدراسة مع العديد من الأبحاث والدراسات المنشورة على مستوى العالم.
تأثير حقن عقار (سم البوتيولنيوم) في عضلة المثانة البولية بجرعة 100 أو 200 وحدة لعلاج المثانة المتهيجة المستعصية

رسالة مقدمة من الطبيب محمد عبد الرحمن الحفناوى

توطئة للحصول على درجة الدكتوراه في جراحة المسالك البولية

المشرفون

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جامعة بنها
كلية الطب
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