EVALUATION OF EFFICACY AND SAFETY OF SOLIFENACIN COMPARED TO TOLTERODINE IN OVERACTIVE BLADDER SYNDROME

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OF THE REQUIREMENT FOR THE DEGREE OF

M.D IN **PHARMACOLOGY**

By

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APRIL– 2011

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LIST OF ABBREVIATIONS USED

5-HMT – 5 Hydroxymethyl Tolterodine

AUC – Area Under curve

BMI – Body Mass Index

BPH – Benign Prostatic Hyperplasia

CNS – Central Nervous System

DEO – N-desmethyloxybutynin

DO – Detrusor Overactivity

FVC – Frequency Volume Chart

ICS – International Continence Society

OAB – Overactive Bladder

OAB-SCS – Overactive Bladder symptom composite score

PGI-I – Patient global impression on improvement

PVRV – Post Void Residual Volume

TCA – Tricyclic Antidepressant

USG – Ultrasonography

UTI – Urinary tract infection

UUI – Urinary urge incontinence

ABSTRACT

Background/Objectives:

To compare the efficacy and safety profile of Solifenacin with Tolterodine in Overactive Bladder Syndrome.

Materials and Methods:

Relevant data were collected from patients with OAB Syndrome, presenting to Department of Urology at R.L.Jalappa Hospital and Research Centre from December 2008 to May 2010. A total of 60 patients were enrolled in the study and written informed consent was taken from all the patients. Patients were randomized into 2 groups of 30 each to receive either oral Tolterodine 4mg or Solifenacin 5mg OD. Both the drugs were administered for a period of 8 weeks and the patients were followed up at 2, 4 and 8 weeks and assessed for efficacy and safety of the drug. Assessment of symptom and quality of life was done using OAB-SCS and PGI-I scale respectively at baseline and each follow up visits. Ultrasonography was done to assess the post voiding residual volume of urine. Laboratory Investigations included RBS, urine analysis, ultrasound examination of bladder and prostate, X-ray KUB and urodynamic evaluation as and when required.

Results:

A comparison of PVRV showed a significant reduction in residual volume with Solifenacin which was similar to Tolterodine. When OAB-SCS and PGI-I scores were compared, both the treatments showed significant reduction in OAB symptoms and improvement in quality of life within the groups at every follow up visit.

Solifenacin produced a greater reduction in OAB-SCS and PGI-I scores compared to Tolterodine at all follow up visits but the reduction was statistically significant only at 2 weeks. Anticholinergic side effects were infrequent and mild in nature.

Conclusion:

Solifenacin 5 mg once daily improved urgency and other symptoms of OAB and was associated with an acceptable level of anticholinergic side-effects in treating symptomatic overactive bladder.

Keywords: Solifenacin; Tolterodine; Overactive bladder.

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INTRODUCTION

Overactive Bladder Syndrome (OAB) is characterized by symptoms of urinary urgency, frequency and /or nocturia with or without urge incontinence. It can affect individuals of all ages with significant and detrimental impact on health related quality of life, mental health and reduced ability to perform daily tasks.[1]

OAB is presumed to be caused by involuntary contractions by the detrusor muscle which is mediated by the action of acetylcholine at muscarinic receptors particularly M_3 receptor subtype.[2] Although treatment approaches to OAB can include behavioral, pharmacological and surgical interventions, pharmacological management remains the mainstay of therapy. [3]

Among the available agents muscarinic receptor antagonists are the treatment of choice. Tolterodine was the first antimuscarinic agent to be specifically developed for the treatment of OAB. It has been demonstrated to have functional selectivity for muscarinic receptors in the urinary bladder over salivary glands, therefore it is associated with lesser adverse effects like dry mouth.[4]

Solifenacin is a newer bladder selective muscarinic (M_1 and M_3) receptor antagonist with greater selectivity for bladder over salivary glands compared to Tolterodine .[5] It has shown to improve symptoms of OAB and increase functional bladder capacity to a significantly greater extent .[6]

As there is a paucity of comparative studies between Solifenacin and Tolterodine in the treatment of Overactive Bladder Syndrome, the present study is undertaken.

AIMS AND OBJECTIVES

1. To compare the efficacy of Solifenacin with Tolterodine in Overactive Bladder syndrome.
2. To compare the safety profile of Solifenacin with Tolterodine in Overactive Bladder syndrome.

REVIEW OF LITERATURE

Overactive Bladder is defined by International Continence Society (ICS) as urgency, with or without urge incontinence, usually with frequency & nocturia in the absence of local pathologic or endocrine factors.[7] Overactive Bladder (OAB) is not a specific disease but a relatively recently coined umbrella term used to describe a collection of symptoms experienced by the patient.

TERMINOLOGY

Overactive bladder is a newly described condition. It was first alluded to by Dubley in 1905 when he distinguished between active and passive incontinence due to sphincter weakness. In 1917, Taylor and Watt reported the importance of urgency as a symptom during history taking to distinguish incontinence with or without urgency. Bates and colleagues introduced the term unstable bladder in 1970 when they used cinecystourethrography to investigate urge incontinence. The term OAB was introduced for use in 1996, as an alternative to unstable bladder. [8]

EPIDEMIOLOGY

Overactive Bladder is a common problem worldwide. It is a chronic and sometimes incapacitating condition suggestive of lower urinary tract dysfunction and one that is becoming increasingly recognized in clinical practice. The prevalence of OAB accounts to 16% of the world wide population, of this only 37% of patients report their symptoms to a health care provider.[9]

Gender Differences in OAB

Although men and women have the same prevalence of OAB overall i.e. 16% & 16.9% respectively, men were shown to have higher prevalence of "OAB dry" (OAB without urge incontinence) over "OAB wet" (OAB with urge incontinence).[10]

Relationship of Age to OAB

Overactive bladder can affect individuals of all ages. An estimated 10 million people of 40 years or older have symptoms consistent with overactive bladder. The incidence of OAB increases with age and the associated quality of life and social issues are well documented. Prevalence of OAB increases similarly with age in both men & women, although in women the prevalence of OAB increases from 2% in young age (18 to 24yrs) to 19.1% in those beyond 65yrs of age. Men on the other hand experience an increase in prevalence of OAB at an older age.[11]

Urinary incontinence affects 30% of the community-dwelling geriatric population (aged 60years and older) and approximately half of those living in nursing homes.[12,13] Paradoxically in the elderly population, the misconception that leakage is an unavoidable part of aging may lead to substantial under reporting of incontinence and other symptoms.[14]

Relationship of Obesity to OAB

In women, the prevalence of wet OAB has been shown to be positively related to increasing body mass index (BMI). Wet OAB is 2.2 times more prevalent in women with a BMI of 30 or more than in those with a BMI under 24.[15]

Body mass index, childbearing, previous hysterectomy and thyroid problems have all been implicated as risk factors for developing OAB.[16,17]

ANATOMY OF THE URINARY BLADDER

The urinary bladder is a musculomembranous sac which acts as a reservoir for the urine. Its size, position and relations vary according to the amount of fluid it contains and the state of the surrounding viscera. When empty it is somewhat tetrahedral and has a base (fundus), neck, apex, a superior and two inferolateral surfaces and lies entirely in the lesser pelvis. As it distends it expands anterosuperiorly into the abdominal cavity. [18]

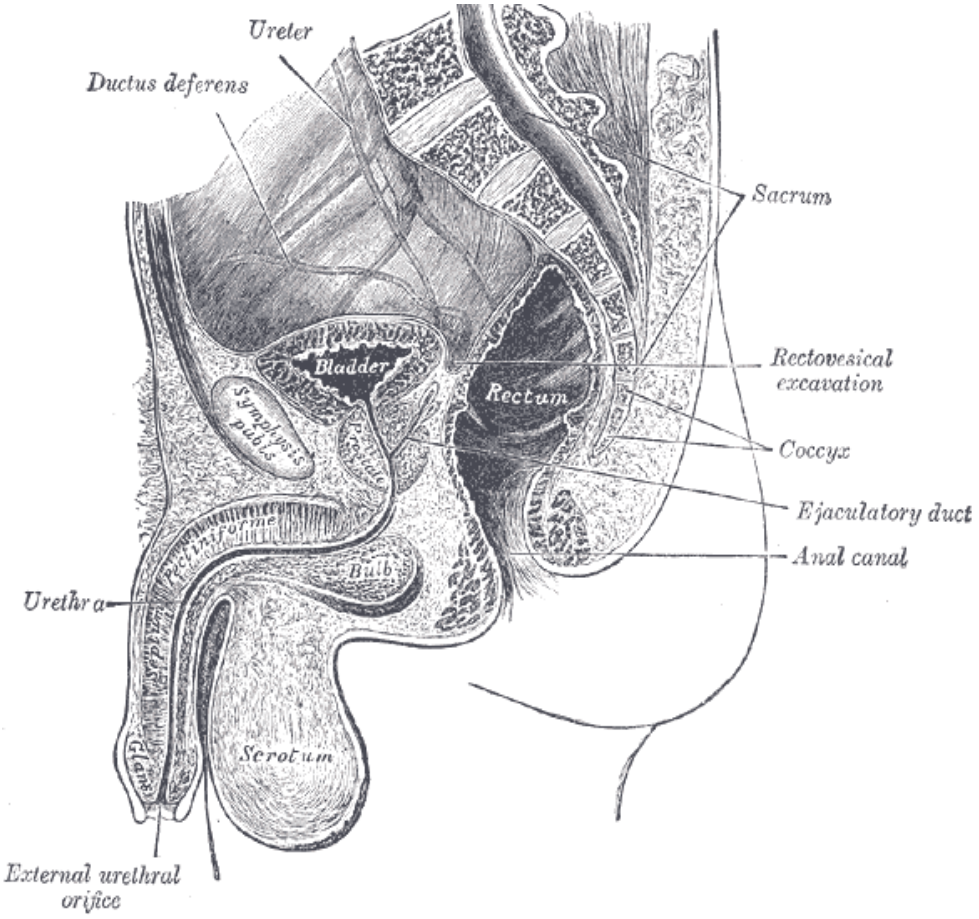


FIGURE 1

(section of male pelvis)

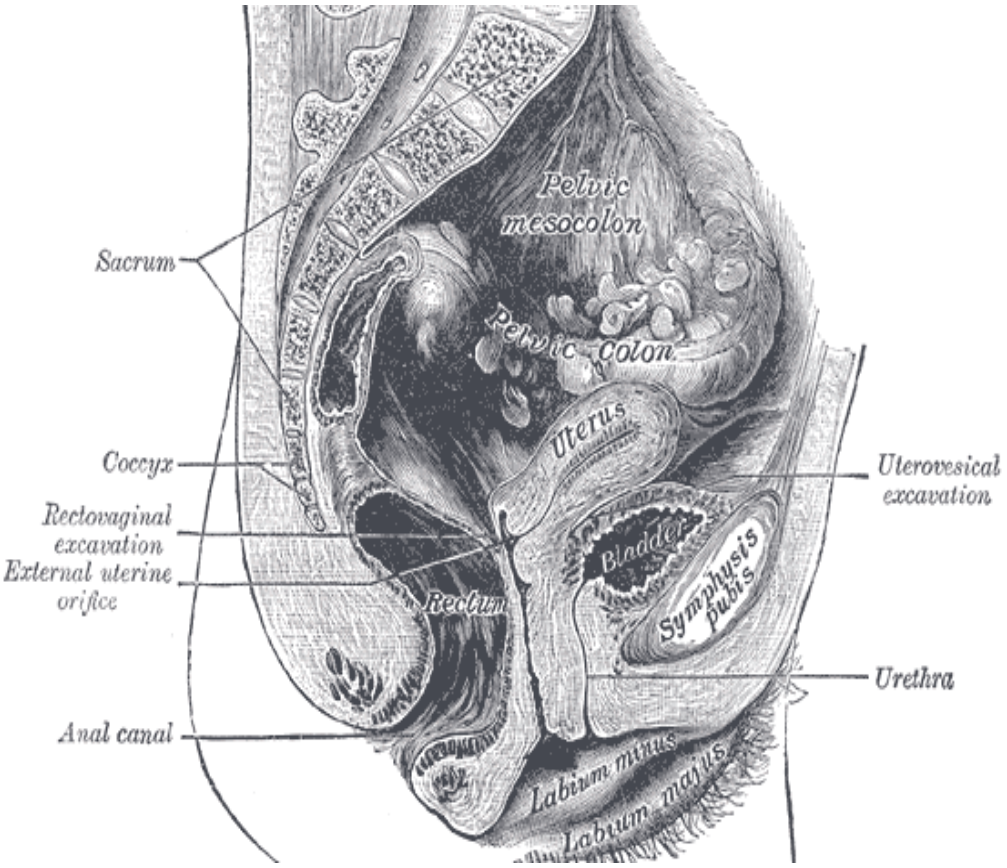


FIGURE 2

(section of female pelvis)

Normal Bladder Capacity:

Normal bladder capacity is between 400 to 600cc. The urinary bladder can normally hold 250 to 350cc of urine before the urge to void becomes conscious. Urinary continence is maintained as long as the pressure within the urethra (intra-urethral pressure) remains higher than the pressure within the cavity of the bladder (intravesical pressure).[19]

The bladder is composed of four coats: serous, muscular, submucous and mucous coats.

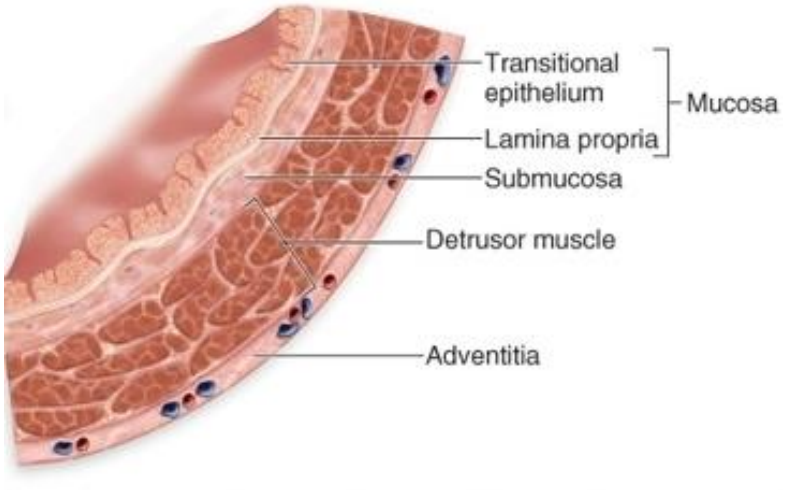


FIGURE 3

(i) The serous coat (tunica serosa) also known as Adventitia is a partial one and is derived from the peritoneum. It invests the superior surface and the upper parts of the lateral surfaces and is reflected from these on to the abdominal and pelvic walls.

(ii) The muscular coat (tunica muscularis) consists of three layers of:

a) External layer: composed of fibres having a longitudinal arrangement

b) Middle layer: in which the fibres are arranged in a circular manner

c) Internal layer: in which the fibres have a longitudinal arrangement.

The fibres of the external layer arise from the posterior surface of the body of the pubis. They pass in a more or less longitudinal manner, up the inferior surface of the bladder, over its vertex and then descend along its fundus to become attached to the prostate in the male and to the front of the vagina in the female. At the sides of the bladder the fibres are arranged obliquely and intersect one another. This layer has been named the "Detrusor muscle".[20]

(iii) The submucous coat (tela submucosa) consists of a layer of areolar tissue, connecting

together the muscular and mucous coats and intimately united to the latter.[20]

(iv) The mucous coat (tunica mucosa) is thin, smooth and of a pale rose colour. It is continuous above with lining membrane of the renal tubules and below with that of the urethra. The area of the mucous membrane covering the internal surface of the base of the bladder is referred to as "Trigone".[20]

The epithelium covering the urinary bladder is of the transitional variety which is stratified comprising three to six layers of cells.[21]

NORMAL BLADDER PHYSIOLOGY

The urinary bladder can be described as a hollow bag made of smooth muscle fibres of detrusor muscle. The Urethra makes an angle with the body of the bladder which is physiologically important to maintain continence. The urethra is surrounded by smooth muscle fibres of internal sphincter which are under autonomic control and the external sphincter which is under voluntary control. However in females distinct anatomical sphincters are not well defined.[18]

INNERVATION OF THE BLADDER

The nerves supplying the bladder arise from the pelvic plexus which are a mesh of autonomic nerves and ganglia on the lateral aspects of the rectum, internal genitalia and bladder base. They consist of both sympathetic and parasympathetic components, each of which contains efferent and afferent fibres.

Parasympathetic fibres arise from the second to the fourth sacral segments of the spinal cord and enter the pelvic plexus on the posterolateral aspect of the rectum as the pelvic splanchnic nerves or Nervi erigentes. The Sympathetic fibres are derived from the lower three thoracic and upper two lumbar segments of the spinal cord.

These form the celiac and mesenteric plexus around the great vessels in the abdomen from which the hypogastric plexus descend into the pelvis as fairly discrete nerve bundles within the extraperitoneal connective tissue posterior to the urethra on each side.

The human detrusor muscle possesses a dense supply of parasympathetic nerves compared to sympathetic nerves which generally accompany the vascular supply and rarely extend among the myocytes. The lamina propria of the fundus and inferolateral walls of the bladder is virtually devoid of autonomic fibres apart from some nor-adrenergic and occasional presumptive cholinergic perivascular nerves.

Vesical nerves are also concerned with pain and awareness of distension and are stimulated by distension or spasm.[22]

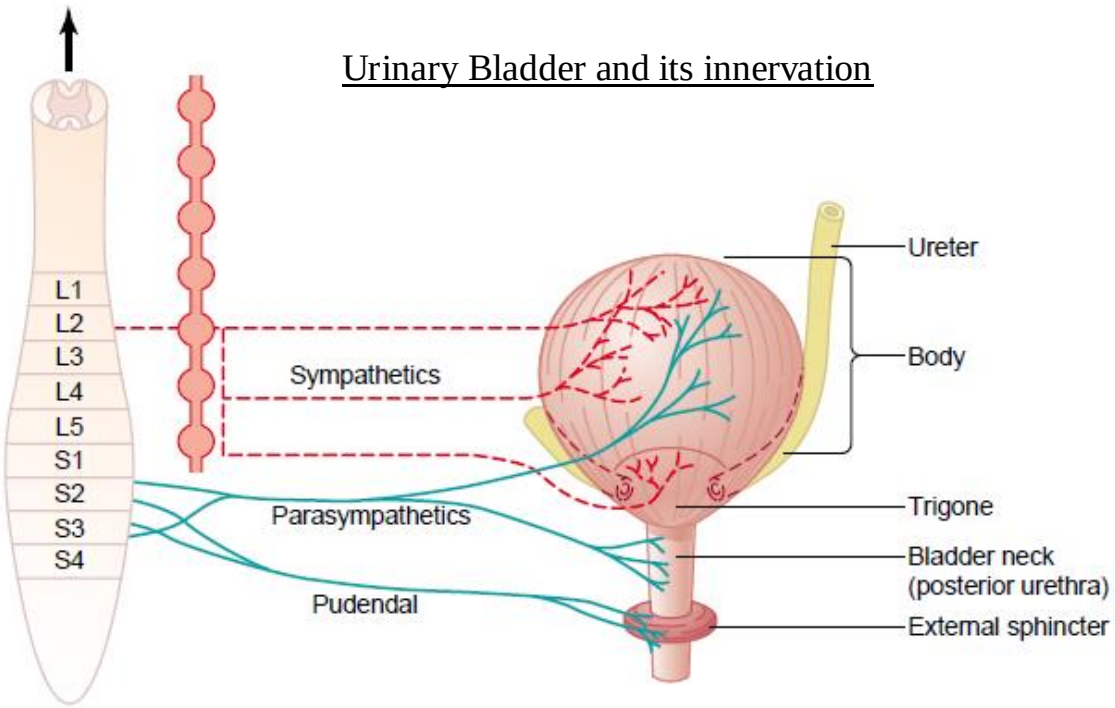


FIGURE 4

Functional role of muscarinic receptors in the urinary bladder:

Detrusor smooth muscle is endowed principally with M_2 and M_3 muscarinic receptors with the former predominating in number. M_3 muscarinic receptors mediate the direct contractile effects of acetylcholine in the detrusor; while M_2 muscarinic receptors cause smooth muscle contraction indirectly by inhibiting sympathetically mediated relaxation. Other contractile mechanisms involving M_2 muscarinic receptors, such as activation of a non-specific cationic channel and inactivation of potassium channels, may also be operative in the bladder and requires further investigation.[23]

MECHANISM AND CONTROL OF MICTURITION

Micturition is the process by which the urinary bladder empties when it becomes filled. It consists of -

1) Storage phase where the bladder fills progressively until the tension in its walls rises above a threshold level

2) Voiding phase which includes a nervous reflex called the micturition reflex that empties the bladder.[24]

Micturition reflex is a stretch reflex initiated by sensory stretch receptors in the bladder wall, especially by the receptors in the posterior urethra. At the higher bladder pressures sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the pelvic nerves and then reflexively back again to the bladder through the parasympathetic nerve fibres by way of these same nerves. Once a micturition reflex begins it is "self-regenerative". Then after a few seconds to more than a minute, the self-regenerative reflex begins to fatigue and the regenerative cycle of the micturition reflex ceases, permitting the bladder to relax. The micturition reflex is a completely autonomic spinal cord reflex, but it can be inhibited or facilitated by centers in the brain which are located in the pons and cerebral cortex.[25]

Thus one can voluntarily delay the micturition reflex or abruptly stop the flow of urine or initiate micturition when bladder is not completely filled. The two major populations of afferent fibres mediating the micturition reflexes are myelinated Aδ-fibres and unmyelinated C fibres. As a general rule, the Aδ-fibres respond to passive bladder distension and active bladder contraction thus conveying information about bladder filling. They are probably responsible for the sensation of fullness and mediate the normal bulbospinal reflex. In contrast the C fibres respond primarily to thermal stimulus or chemical irritation of the bladder mucosa.[24]

PATHOPHYSIOLOGY OF OVERACTIVE BLADDER

The symptoms of OAB are usually associated with involuntary contractions of the detrusor muscle, defined as Detrusor Overactivity (DO) which occurs as the urinary bladder fills. The cause of this is unknown. In theory, Overactive Bladder might rise in circumstances in which the afferent activity is inappropriately high for any given degree of bladder distension. This could arise if nerve endings are pathologically sensitized or if they are abnormally numerous. Several hypothesis have been proposed to explain the pathophysiological basis of detrusor overactivity.

The Neurogenic hypothesis:

The neurogenic hypothesis states that the detrusor overactivity arises from generalized nerve mediated excitation of the detrusor muscle. Several interdependent mechanisms by which they arise are

- Damage to the brain which can induce detrusor overactivity by reducing suprapontine inhibition.
- Damage to axonal pathways in the spinal cord which allows the expression of primitive spinal bladder reflexes.

- Synaptic plasticity leading to reorganization of sacral activity with the emergence of new reflexes which may be triggered by C-fibre bladder afferent neurons.
- Sensitization of peripheral afferent terminals in the bladder which can trigger detrusor overactivity.[26]

The Myogenic hypothesis:

This hypothesis suggests that overactive detrusor contractions result from a combination of an increased likelihood of spontaneous contraction and enhanced propagation of activity between muscle cells. Patchy denervation is a common observation in detrusor overactivity, regardless of etiology. A smooth muscle cell deprived of its innervation shows an up-regulation of surface membrane receptors which increases the likelihood of spontaneous contraction in that cell.

Detrusor overactivity is also associated with characteristic changes in the ultrastructure which could facilitate the propagation of the contraction over a wider proportion of the body of the detrusor than normal and thus can show altered responsiveness to nervous and pharmacological stimuli.[27]

Peripheral Autonomy hypothesis:

The peripheral autonomy hypothesis suggests that increased bladder sensation results from exaggerated localized modular contraction. Detrusor overactivity is due to enhanced coordination of modular activity through the myovesical plexus. A module is the smallest functional unit of detrusor muscle which is a circumscribed area of muscles, each of which is defined by elements within the myovesical plexus. The activity in individual modules would have very little effect on intravesical pressure but synchronization of activity in neighboring modules would lead to contraction of a more substantial proportion of the bladder wall, resulting in measurable intravesical pressure effects. [28]

CAUSES OF OVERACTIVE BLADDER:

Specific identifiable causes:

- nerve damage caused by injury, pelvic surgery or repeated pregnancies.
- neurological diseases (e.g. Diabetic neuropathy, multiple sclerosis, Parkinson's disease, spinal cord lesions, spina bifida, stroke)

Other identifiable causes of overactive bladder symptoms include:

- urinary tract infections, radiation cystitis
- bladder cancer
- benign prostatic hyperplasia (BPH)
- stones in the bladder
- constipation (stool impaction)
- pelvic organ prolapse
- bladder injury (e.g. Road traffic accidents)
- Diet and lifestyle (spicy food, alcohol and caffeine may irritate the bladder).[29]

CLASSIFICATION OF DETRUSOR OVERACTIVITY

Detrusor overactivity (DO) can be phasic or terminal / idiopathic or neurogenic

- Phasic DO: it is defined by a characteristic wave form and may or may not lead to urinary incontinence
- Terminal DO: it is defined as a single, involuntary detrusor contraction, occurring at cystometric capacity, that cannot be suppressed and results in incontinence, usually leading to bladder emptying (voiding)

According to cause-

- Neurogenic DO: it is the term used when there is a relevant neurological condition
- Idiopathic DO: it is the term used when there is no defined cause. [30]

CLINICAL ASSESSMENT

History:

Because OAB is a symptomatic diagnosis, history plays an important part in assessing the patient. The purpose of the clinical history is to have an empiric diagnosis, to exclude other causes for the patient's symptoms and to assess the effects of problem on the patient's daily activities that would help in deciding the treatment strategy. Questions should include details of the following:

- Nature and duration of symptoms
- Previous medical or surgical treatment for the condition
- History of radiation exposure and Environmental issues
- Patient mobility and Mental status
- Other neurological condition (stroke, trauma)
- Sexual function
- Bowel function (as irritable bowel syndrome can be associated with OAB)
- Gynaecologic and obstetric history
- Current management, including pad usage
- A symptom index of benign prostatic hypertrophy as recommended by American Urological Association or International prostatic symptom score (IPSS).[31,33]

Symptoms

The symptoms of overactive bladder are urgency, frequency, nocturia, with or without urgency incontinence.Patients may have some or all of these symptoms. Overactive bladder is either of OAB dry or OAB wet type.[31]

Urgency is a sudden urgent need to urinate which one cannot postpone. Urgency is not the same as the gradual normal desire to urinate when the bladder is becoming full. In a normal bladder, the first sensation of fullness is felt when the bladder is filled to about half its capacity. Urgency may occur when there are just a few drops of urine in the bladder.

Urge incontinence is urgency followed by involuntary leakage of urine before reaching the toilet. This may be a small loss of a few drops of urine or the bladder may empty completely.

Frequency can be divided into daytime frequency and night time frequency (nocturnal frequency). Daytime frequency is "the number of voids recorded during waking hours and includes the last void before sleep and the first void after waking and rising in the morning".

Nocturia is "the complaint that the individual has to wake at night one or more times to void".[8, 32]

Quantification of symptoms:

1. Questionnaires:

They are used to assess quality of life in relation to the symptoms. In theory, validated questionnaires can be used for making a diagnosis, as a tool in prevalence study and to measure the outcome of the treatment.[34]

1. BSW Questionnaire

The BSW consists of three, single-item, patient-rated, interviewer administered, global assessments of treatment Benefit, Satisfaction with treatment and Willingness to continue treatment.

2. Nocturia Quality of Life (N-QOL) Questionnaire

The N-QOL is a 13-item, 5-point scale that asks patients to rate their subjective impression of the impact of "having to get up at night to urinate" on their quality of life.

3. The Overactive Bladder Questionnaire (OAB-q)

The OAB-q was developed to assess the symptom bother and health-related quality of life (HRQL) impact of overactive bladder (OAB) on patients' lives. The 33-item OAB-q consists of an 8-item symptom bother scale and 25 items health-related quality of life (HRQL) items. The 25 HRQL items comprise 4 subscales (concern, coping, social interaction, sleep).

4. The Overactive Bladder Questionnaire Short Form (OAB-q SF)

A shortened version of the OAB-q was derived from the original questionnaire through item response theory analyses. This "short form," called the OAB-q SF, consists of a 6-item symptom bother scale and a 13-item HRQL scale. The OAB-q SF has been included in the International Consultation on Incontinence Modular Questionnaire (ICIQ-OAB) module to assess the impact of OAB on patients' lives. The OAB-q SF has demonstrated good internal consistency reliability, concurrent validity, discriminant validity and responsiveness.

5. Overactive Bladder Family Impact Measure (OAB-FIM) Questionnaire

The Overactive Bladder Family Impact Measure (OAB-FIM) is the first validated instrument designed to assess the impact of OAB on family members' quality of life. This 19-item questionnaire has four subscales (Irritation, Activities, Travel, Concern) intended for use among all family members as well as two additional subscales (Sleep, Sex) for use only by spouses/guardians of OAB patients.

6. *Patient Perception of Bladder Condition (PPBC) Questionnaire*

The PPBC is a single-item, 6-point scale that asks patients to rate their subjective impression of their current bladder problems.[34]

2. Fluid input/output charts:

Micturition events can be recorded in three main forms –

a) Micturition time chart: records only the times of micturition for a period of 24hrs.
b) Frequency-volume chart (FVC): records the volumes voided as well as the time of each micturition for a period of 24hrs.
c) Bladder diary: records the times of micturations and voided volumes, incontinence episodes, pad usage and other information such as fluid intake, degree of urgency and degree of incontinence.[35]

Examination:

In addition to the general examination, a focussed clinical examination should be carried out that includes –

- Abdominal examination: for distended bladder
- Neurological examination: signs of any neurological deficits
- Rectal examination: to assess anal tone , pelvic floor function and prostate size
- External genitalia and perineal examination
- Vaginal examination (in females): to assess pelvic organ prolapse.[35,36]

Simple investigations

Urine analysis: to detect urinary tract infection

Urinary tract imaging: USG or plain radiographic study can be done to look for

- Lower urinary tract or pelvic pathologies
- Estimate post void residual volume (PVRV) of urine.[37]

Invasive investigations

Endoscopy:

Flexible or rigid cystoscopy has a limited role in patients with pure symptoms of OAB unless other pathology is suspected. Endoscopy is recommended in the following situations-

- When initial testing suggests other pathologies such as microscopic hematuria (possibility of bladder tumour)
- When pain or discomfort occurs in a patient with OAB (suggesting a intravesical lesion).[38]

Urodynamic evaluation:

There is some controversy in regard to the use of urodynamics testing in patients with lower urinary tract symptoms, particularly those with OAB, based on several issues like-

a) Urodynamics is an invasive test with possible side effects, mainly UTI
b) The test is uncomfortable and could be embarrassing for the patient
c) The test has a considerable false-negative rate

It is recommended in the following situations-

a) Before invasive treatments
b) After conventional treatment failure to assess the exact nature of bladder dysfunction causing overactivity.
c) As a part of along term surveillance program in neurogenic OAB
d) In complicated incontinence

The aims of routine urodynamics evaluation are-

- The detection of detrusor overactivity
- The assessment of urethral competence during filling
- The determination of detrusor function during voiding

- The assessment of outlet function during voiding
- The measurement of residual volume of urine

Urodynamics data in a patient with detrusor overactivity is characterised by involuntary detrusor contractions during the bladder filling that may be spontaneous or provoked. Provocative maneuvers are defined as techniques used during urodynamics in an effort to provoke detrusor overactivity, such as rapid filling, use of cool or hot medium and postural changes.[38, 39]

TREATMENT

The principles of treatment include increasing voided volume, decreasing urgency and reducing urine urge incontinence episodes. Various treatment modalities include –

- Conservative management
- Pharmacotherapy
- Surgery

A. CONSERVATIVE MANAGEMENT

1. Life style interventions: include

i. Patient and attendant education about OAB.[40]

ii. Diet modification is aimed at excluding any food or drink that appears to irritate the bladder or which may act as a diuretic to produce more urine (eg caffeine, alcohol, carbonated drinks, tomato-based products, chocolate, artificial sweeteners and spicy foods. Since constipation can exacerbate OAB symptoms, sufficient high fibre food must be consumed. Fluids should be avoided after 9.00 PM and voiding before going to bed in case of history of nocturia must be practised.[41]

2. Bladder training and pelvic floor exercises:

It generally refers to a combination of patient education, scheduled voiding and urge suppression techniques and pelvic muscle exercises. The patients are taught to void regularly and then asked to increase the interval between voids by 15 minutes each week over a period of around 12 weeks until they feel comfortable with their urinary frequency. "Kegel" or pelvic muscle exercises can strengthen muscles around the bladder and urethra thereby improving bladder control and reducing urgency/frequency, while at the same time strengthening other pelvic muscles that hold many other organs in place. Pelvic floor exercises include teaching the patient to tighten the pelvic floor when sitting-up from lying down and when standing-up from a sitting position.[42]

Biofeedback and/or electrical stimulation does not seem to add to efficacy as compared to bladder training alone; however, these methods can be used only as an adjunct to bladder training in selected patients.[43]

B. PHARMACOTHERAPY

Many classes of drugs have been studied or proposed for the medical treatment of overactive bladder. With the presently available drugs, medical therapy aims to –

1. Inhibit bladder contractility (anticholinergic agents, musculotrophic agents and tricyclic antidepressants)
2. Increase outlet resistance (alpha adrenergic agonists)
3. Decrease urine production (desmopressin)
4. Improve local tissue health (estrogens).[44]

1. Anticholinergic or Antimuscarinic Drugs:

Anticholinergic/antimuscarinic drugs are the mainstay of drug treatment for overactive bladder. These drugs block muscarinic receptor on the detrusor muscle that is stimulated by acetylcholine released by activated cholinergic nerves; thereby decrease the ability of the bladder to contract. However antimuscarinic drugs act on the storage phase, decreasing urgency and increasing bladder capacity. Undeniably, high doses of antimuscarinics can eventually produce urinary retention.[45]

In general, antimuscarinics can be divided into tertiary and quaternary amines with regard to their lipophilicity, molecular charge and to a lesser extent to their molecular size. Tertiary compounds generally have greater lipophilicity and lesser molecular charge than quaternary agents. Atropine, tolterodine, oxybutynin, propiverine, solifenacin and darifenacin are tertiary amines that are well absorbed orally and are capable of crossing the blood brain barrier. Whereas quaternary ammonium compounds, like propantheline and tropsium, are not well absorbed orally and pass into the CNS to a limited extent and have a low reported CNS side effects.[46]

Antimuscarinics are still the most widely used treatment for urgency and urge incontinence. Efficacy of these drugs is dose-dependent, but effectiveness is often limited by unwanted antimuscarinic effects in distant organs which commonly include dry mouth, dry eyes, confusion, constipation, somnolence, blurred vision and increased heart rate.[47]

Atropine:

Atropine (dl-hyoscyamine) is rarely used for treatment of OAB because of its systemic side effects which precludes its use. However, in patients with neurogenic detrusor overactivity, intravesical atropine may be effective for increasing bladder capacity without causing much systemic adverse effects.[48]

Propiverine:

Propiverine is a tertiary amine. It is rapidly absorbed but has a high first pass metabolism. The half life of the parent compound is about 11-14 hours. It has shown to have a combined anti-muscarinic and calcium antagonistic properties. Effective at a dose of 15mg twice or thrice daily.[49]

Fesoterodine:

Fesoterodine is a new antimuscarinic agent for treating overactive bladder. It acts functionally as a pro-drug and is rapidly and extensively converted by non-specific esterases to its primary active metabolite, 5-hydroxymethyl tolterodine (5-HMT). 5-HMT is also the major active metabolite of tolterodine, but it is formed from tolterodine via CYP2D6-mediated oxidation in the liver. Because Fesoterodine does not require CYP2D6 metabolism for activation, it has the potential for less drug interaction. Maximum recommended dose is 8mg once daily.[50]

Darifenacin:

Darifenacin is a tertiary amine with moderate lipophilicity, well absorbed from the gastrointestinal tract after oral administration and extensively metabolised in the liver by cytochrome P-450 isoforms CYP3A4 and CYP2D6. Darifenacin has been developed as a controlled release formulation which allows once daily dosing. Recommended doses are 7.5 and 15mg/day. Darifenacin is a relatively selective muscarinic M3 receptor antagonist. The most common adverse effects were mild to moderate dry mouth and constipation.[51]

Propantheline:

Propantheline bromide is a quaternary ammonium compound non selective for muscarinic receptor subtypes, that has low (5-10%) and individually varying bioavailability.

It has a short plasma half life of < 2hrs. Usually given in a dose of 15 to 30mg four times daily, but to obtain an optimal effect, individual titration of the dose is required.[52]

Tropsium:

Tropsium chloride is a quaternary ammonium compound with a bioavailability of less than 10%. It is expected to cross the blood brain barrier to a limited extent and seems to have no negative cognitive effects. The drug has a plasma half life of approximately 20 hrs and is mainly eliminated unchanged in the urine by renal tubular secretion. It is not metabolised by cytochrome P-450 enzyme system. Tropsium has no selectivity for muscarinic receptor subtypes. Tropsium is effective at a dose of 20mg given twice daily. At this dose it significantly decreases frequency of toilet voids, urgency incontinent episodes, average urgency severity and day time frequency and significantly increases average volume per void.[53]

2. **Musculotrophic Relaxants.**

All of these agents relax smooth muscle in vitro and all possess variable amounts of anticholinergic and local anaesthetic properties. The amount of atropine like activity in the clinical efficacy of these drugs is unknown. Side effects are common and are similar to those of anticholinergic agents.

Oxybutynin:

Oxybutynin is a tertiary amine that is well absorbed orally and undergoes extensive upper gastrointestinal and first pass metabolism via cytochrome P-450 system (CYP3A4) into multiple metabolites. The primary metabolite is N-desmethyloxybutynin (DEO) which has pharmacological properties similar to that of parent compound. Plasma half life is approximately 2 hr. It is a non-selective antimuscarinic agent that relaxes the bladder muscles and has local anaesthetic activity.

The anaesthetic property may be of importance when the drug is administered intravesically but probably does not have a role to play when administered orally. Oxybutynin has been shown to have a high affinity for muscarinic receptors in the bladder and has a higher affinity for M_1 and M_3 receptors over M_2. [54]

Formulations of oxybutynin:

1. Immediate-release oxybutynin:

The immediate release (IR) form of oxybutynin is recognised for its efficacy and the newer agents are compared with it for its efficacy. The recommended dose of immediate release oxybutynin is 5mg three or four times daily. Several studies have shown that the therapeutic effect of oxybutynin IR on detrusor overactivity is associated with higher incidence of antimuscarinic side effects. It is available as immediate release (5 mg TID).[55, 56]

2. Extended release oxybutynin

More recently a controlled release oxybutynin preparation using an osmotic system (OROS) has been developed which has been shown to have comparable efficacy to immediate release Oxybutynin. This formulation was developed to decrease metabolite formation of DEO with the presumption that it would result in decreased side effects, especially dry mouth and improve patient compliance with oxybutynin therapy. The osmotic system helps to release the drug distally into the large intestine at a controlled rate during 24hrs or more. Available as 5 and 10mg ER tablets for once daily administration.[57]

3. Transdermal oxybutynin

An oxybutynin transdermal delivery system has recently been developed which is shown to significantly reduce incontinence episodes, increased volume voided and an improvement in quality of life.

This formulation also alters oxybutynin metabolism, reducing DEO production to an even greater extent than oxybutynin ER. The most common adverse event in the oxybutynin patch is application site pruritus, although the incidence of dry mouth is reduced. Available as transdermal patches (39 cm^2 patch in a dose of 36 mg per patch) with a release of 3.9 mg of oxybutynin per day over 3 - 4 days [58]

4. Oxybutynin bladder pump

A bladder pump is under development that releases oxybutynin at a constant rate over 30 days, improving upon the need for multiple daily catheterisations to administer the drug intravesically. Oxybutynin is released directly into the bladder at a constant micro molar dose, eliminating systemic effects. The device would be placed via catheterisation and removal would require cystoscopy. This innovative therapy has additional applications in delivery of other bladder medications such as chemotherapy for bladder cancer.[59]

Dicyclomine hydrochloride:

It has similar properties to oxybutynin chloride. Dosage is 10 mg to 20 mg, three to four times daily.[60]

Flavoxate hydrochloride:

It is a tertiary amine with smooth-muscle relaxant properties and weak anticholinergic activity. It is used for the symptomatic relief of pain, urinary frequency and incontinence associated with inflammatory disorders of the urinary tract. It is also used for the relief of vesicourethral spasms resulting from instrumentation or surgery. Flavoxate is readily absorbed from the gastrointestinal tract and rapidly metabolised, about 50 to 60% of a dose being excreted in the urine within 24 hours as methyl flavone carboxylic acid. Dosage is 200 mg three to four times daily. Adverse effects are said to be less marked than those seen with other antimuscarinics such as oxybutynin.[60]

3. Tricyclic Antidepressants (TCAs):

Tricyclic antidepressant with both anticholinergic and alpha-adrenergic effects and possibly a central effect on voiding reflexes have been recommended for mixed urge-stress incontinence. TCAs block the active transport of norepinephrine into the adrenergic nerve terminal potentiating contraction of the bladder base and the proximal urethra (and possibly beta-receptor induced relaxation of the bladder body). There may also be a direct inhibitory effect on the bladder muscle. Imipramine hydrochloride is useful alone or in combination with other anticholinergics, but the side effects may be additive. Dosage is 10 mg to 25 mg one to four times daily. Doxepin has also been tried at a dose of 50mg.

Their role in detrusor overactivity remains uncertain although they are often useful in patients complaining of nocturia and bladder pain. These drugs must be used with caution in the elderly due to the risk of orthostatic hypotension and ventricular arrhythmia.[61]

4. Alpha-adrenergic antagonists

Even if it is well known that alpha adrenergic receptor antagonists can ameliorate lower urinary tract symptoms in men with benign prostatic hyperplasia, there are no controlled clinical trials showing that they are effective in the treatment of OAB- detrusor overactivity. In addition, in women these drugs may exacerbate or result in stress incontinence. However alpha adrenergic antagonists have been used in the treatment of neurogenic bladder with moderate success.[62]

5. Antidiuretic hormone-like agents*:*

Desmopressin is a synthetic vasopressin which has a potent antidiuretic effect. It is being used in the management of diabetes insipidus and nocturnal enuresis. More recently it has been shown to be effective in reducing nocturia in patients with both neuropathic and non-neuropathic bladders. Recent studies have also demonstrated benefit in daytime urinary frequency and urinary incontinence.

Adverse effects may include headache, rhinitis, nasal discomfort, epistaxis and abdominal pain. Water retention may be caused by overdosage.[63]

6. Estrogens:

Estrogens have been used to treat postmenopausal urgency and urge incontinence for many years. It has shown to improve maturation index of urethral squamous epithelium, increases urethral closure pressure and improve abdominal pressure transmission to the proximal urethra. In addition the sensory threshold of the bladder may also be raised. Thus it has proven to be useful for the treatment of overactive bladder in females which results due to deficiency of estrogen. It may be administered either by topical cream or orally 3mg daily or as an implant (25mg of 17β-estradiol implant).[64] It is contraindicated in elderly females due to its carcinogenic effects.

7. Potassium channel opening agents:

The opening of K^+ ion channels in the membrane of the detrusor muscle cell leads to increase in K^+ movement out of the cell resulting in membrane hyperpolarization. This leads to a decrease in calcium influx by reducing the opening probability of Ca^{2+} channels with subsequent relaxation. Two types of potassium channels have been identified in the detrusor muscle: ATP sensitive channels and calcium-dependent large conductance channels. At present the relationship between each of these types of channels and the myogenic, neurogenic and micturition forms of detrusor contraction has not been determined. To date cromakalim, nicorandil and pinacidil have been investigated, although newer agents are currently under development. However their clinical usefulness is limited by significant cardiovascular effects. At present there is no evidence to suggest that K^+ channel openers represent a viable treatment alternative.[65]

8. Calcium channel blocking agents:

Activation of detrusor muscle, through both muscarinic and non adrenergic non cholinergic pathways, requires influx of calcium through Ca^{2+} channels.

Spontaneous and evoked contractile activity is mediated by membrane depolarisation and the movement of calcium into the smooth muscle cell through L-type Ca^{2+} channels. The inhibition of the calcium influx with calcium channel blocking agents such as nifedipine can prevent spontaneous and evoked contractile activity.

Nifedipine and Diltiazem have shown to significantly increase bladder capacity, lower bladder pressure and decrease the number of episodes of incontinence. At present there is insufficient evidence to suggest that calcium channel blocking agents are effective in the treatment of detrusor overactivity. Although the development of a selective calcium channel blocking agent which eliminates spontaneous contractions without affecting micturition may prove to be of use in the treatment of detrusor overactivity.[60]

9. Botulinum toxin (Botox):

Seven immunologically distinct antigenic subtypes of botulinum toxin have been identified: A, B, C1, D, E, F and G of which type A is the most widely used. Botulinum toxin A (Botox) is a purified neurotoxin complex which blocks the release of acetylcholine and other transmitters from presynaptic nerve endings. This results in decreased muscle contractility and muscle atrophy at the injection site. The produced chemical denervation is reversible as axons are regenerated in about 3–6 months. Botox cannot cross the blood–brain barrier and hence has no CNS side effects. According to recent studies, botulinum toxin A (Botox A) intravesical injection into the detrusor muscle or into the detrusor and sphincter in the bladder has so far produced promising results as a form of treatment for OAB that fails to respond to other treatments.

The minimal invasiveness of Botox-A toxin injection in the bladder makes it attractive in the treatment of refractory detrusor overactivity. Improvements have been shown to last for 9-12 months in OAB patients. Side effects have included temporary urinary retention (inability to empty the bladder) in some patients.[66] The cost of Botox injection is very high and the procedure has to be repeated cystoscopically every 6-9 months.

10. <u>Vanilloid substances (Capsaicin and Resiniferatoxin):</u>

Capsaicin is extracted from red-hot chilly peppers and Resiniferatoxin is extracted from Euphorbia resinifera (a cactus-like plant abundant in northern Africa). The receptor targeted by capsaicin and resiniferatoxin is vanilloid receptor type 1 (VR1). In the bladder VR1 is strongly expressed in the membrane of unmyelinated sensory fibres. Additionally VR1 is expressed in smaller amounts in the cell membrane of urothelial cells. Capsaicin and resiniferatoxin administered intravesically causes desensitisation of C fibres which may be responsible for signals that trigger detrusor overactivity. Many clinical trials have shown that intravesical vanilloids increases the bladder capacity at which micturition occurs and reduces urge incontinence. It was found that resiniferatoxin was superior to capsaicin and is associated with lesser discomfort than that of capsaicin.[67]

C. SURGERY

Many different surgical treatments have been tried in the management of detrusor overactivity. Abandoned procedures include bladder distension, vaginal denervation, bladder transection and sacral neurectomy because of an unacceptably high rate of complications and limited efficacy. Surgical solutions for detrusor overactivity include sacral neuromodulation, detrusor myectomy, augmentation cystoplasty or urinary diversion.

Sacral Neuromodulation:

Stimulation of the S3 nerve root by an implanted electrical pulse generator can provide effective relief from frequency and urgency symptoms. Typically it is performed as a staged procedure.

The first stage involves a "test" stimulation using a percutaneous needle to stimulate the S3 nerve root. If there is a favorable response during the trial period then long-term stimulation can be provided by implanting an implantable pulse generator surgically. The implantable pulse generator is usually placed in the fatty tissues overlying the upper outer quadrant of the buttock.[68]

Recent evolutions in this technique now permit a permanent lead to be used for the test stimulation. If the test is unsuccessful the lead can be removed, but if it is successful this lead is attached to the permanent implantable pulse generator. This has the advantage of ensuring that stimulation is provided in the exact location as during the test period. The technique is used for treatment of urinary urgency, frequency, urge incontinence and urinary retention. Complications most commonly reported are generator site pain and implant site pain. Neuromodulation is however very expensive and is not suitable for routine use.[69]

Peripheral neuromodulation:

Peripheral neuromodulation involve stimulating the S3 nerve fibres more peripherally, at the posterior tibial nerve or cutaneous stimulation of the pudendal nerve via an anal or vaginal probe. For the posterior tibial nerve stimulation, a needle is placed percutaneously near the ankle and is attached to an external electrical device. Instead of implanting an implantable pulse generator, the patient returns for periodic sessions often weekly for a series of treatments.[70]

Clam augmentation cystoplasty:

Augmentation cystoplasty is used to increase the size of the urinary reservoir and render the bladder less contractile. It is indicated in patients

a) who lack adequate bladder capacity or detrusor compliance
b) who manifest debilitating frequency and urgency symptoms with urge incontinence
c) urinary tract infections who have failed to derive benefit from medical treatment
d) whose lifestyle is severely limited with high pressure urine storage endangering the upper renal tracts.

The operation most frequently used is the ‘‘clam’’ cystoplasty. In this procedure, the bladder is bisected almost completely and a patch of gut incised longitudinally along the antimesenteric border is sewn in place. This often cures the symptoms of detrusor overactivity by converting a high-pressure system into a low-pressure system although inefficient voiding may result. Patients have to learn to strain to void, or may have to resort to clean intermittent self-catheterisation, sometimes permanently.[71]

Mucus retention in the bladder may also be a complication following this procedure, but this can be partially overcome by ingestion of 200 ml of cranberry juice each day in addition to intravesical mucolytics such as acetylcysteine. The chronic exposure of the ileal mucosa to urine may lead to malignant change. There is a 5% risk of adenocarcinoma arising in ureterosigmoidostomies, where colonic mucosa is exposed to N-nitrosamines found in both urine and faeces and a similar risk may apply to enterocystoplasty.

Biopsies of the ileal segment taken from patients with ‘‘clam’’ cystoplasties show evidence of chronic inflammation of villous atrophy and diarrhoea caused by disruption of the bile acid cycle is common which may be treated using cholestyramine.

The other adverse effects of this procedure include metabolic disturbances such as hyperchloremic acidosis, B12 deficiency and occasionally osteoporosis secondary to decreased bone mineralisation.[72]

Detrusor myectomy:

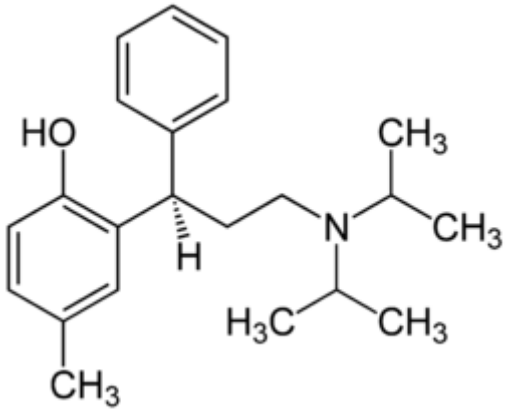
Detrusor myectomy offers an alternative to clam cystoplasty by increasing functional bladder capacity without the complications of bowel interposition.

In this procedure the whole thickness of the detrusor muscle is excised from the dome of the bladder, thereby creating a large bladder diverticulum with no intrinsic contractility. This leads to a reduction in episodes of incontinence but with little improvement in functional capacity and thus frequency remains problematic.[73]

Urinary diversion:

As a last resort for those women with severe detrusor overactivity or neurogenic detrusor overactivity who cannot manage clean intermittent catheterisation it may be more appropriate to perform a urinary diversion. Usually this will utilise an ileal conduit to create an abdominal stoma for urinary diversion. An alternative is to form a continent diversion using the appendix (Mitrofanoff) or ileum (Koch pouch) which may then be drained using self-catheterisation.[71]

TOLTERODINE



Chemistry

Tolterodine is a muscarinic receptor antagonist. The chemical name of tolterodine tartrate is (R) – 2 - [3 - [bis (1-methylethyl) -amino] 1-phenylpropyl] -4- methylphenol2, 3dihydroxy butanedioate (1:1) (salt). The empirical formula of tolterodine tartrate is C26H37NO7 and its molecular weight is 475.6. Tolterodine tartrate is a white, crystalline powder. The pKa value is 9.87 and the solubility in water is 12 mg/mL. It is soluble in methanol, slightly soluble in ethanol and practically insoluble in toluene. The partition coefficient (Log D) between n-octanol and water is 1.83 at pH 7.3.[74]

Mechanism of action

Tolterodine is a competitive muscarinic receptor antagonist with relative functional selectivity for bladder muscarinic receptors. While it shows no specificity for receptor subtypes it does appear to target the bladder over the salivary glands. The drug is metabolised in the liver to the 5-hydroxymethyl derivative which is an active metabolite with a similar pharmacokinetic profile and is thought to contribute to the therapeutic effect. Both tolterodine and the 5-hydroxymethyl metabolite exhibit a high specificity for muscarinic receptors.[75]

Pharmacokinetics

Absorption:

Tolterodine is rapidly absorbed and maximum serum concentrations (Cmax) typically occur within 1 to 2 hours after oral administration. It has a bioavailability of 77%. Food intake increases the bioavailability of tolterodine.[76]

Distribution:

Tolterodine is approximately 96.3% bound to plasma proteins, primarily α1-acid glycoprotein. Unbound concentrations of tolterodine average 3.7% ± 0.13% over the concentration range achieved in clinical studies. The 5-hydroxymethyl metabolite is not extensively protein bound, with unbound fraction concentrations averaging 36% ± 4.0%. The blood to serum ratio of tolterodine and the 5-hydroxymethyl metabolite averages 0.6 and 0.8 respectively, indicating that these compounds do not distribute extensively into erythrocytes. The volume of distribution of tolterodine is 113 ± 26.7 L.[76]

Metabolism:

Tolterodine is extensively metabolised by the liver following oral dosing. The primary metabolic route involves the oxidation of the 5-methyl group and is mediated by the cytochrome P450 2D6 (CYP2D6) and leads to the formation of a pharmacologically active 5-hydroxymethyl metabolite. Further metabolism leads to formation of the 5-carboxylic acid and *N*-dealkylated 5-carboxylic acid metabolites.

Variability in Metabolism:

A subset of the population (about 7%) is devoid of CYP2D6 the enzyme responsible for the formation of the 5-HMT metabolite of tolterodine. The identified pathway of metabolism for these individuals ("poor metabolisers") is dealkylation via cytochrome P450 3A4 (CYP3A4) to N-dealkylated tolterodine. The remainder of the population is referred to as "extensive metabolisers".

Pharmacokinetic studies revealed that tolterodine is metabolised at a slower rate in poor metabolisers than in extensive metabolisers. This results in significantly higher serum concentrations of tolterodine and negligible concentrations of 5-HMT metabolite.[77]

Excretion:

Tolterodine is eliminated 77% in urine and 17% in faeces. The elimination half-life of Tolterodine for both males and females is 2.4 hours and the half-life of the 5-HMT metabolite is 3.0 hours in females and 3.3 hours in males. The pharmacokinetics of tolterodine is not significantly influenced by age and has not been established yet in pregnant, lactating mothers and paediatric patients.[76]

Adverse effects

The most common adverse events reported by patients receiving tolterodine are dry mouth, headache, constipation, vertigo, dizziness, abdominal pain, abnormal vision (accommodation abnormalities), urinary retention and xerophthalmia. Other less common side effects are anaphylactoid reactions including angioedema, tachycardia, palpitations, peripheral oedema, confusion, disorientation, memory impairment and hallucinations. Reports of aggravation of symptoms of dementia (e.g. confusion, disorientation, delusion) have been reported after tolterodine therapy in patients taking cholinesterase inhibitors for the treatment of dementia.[78]

Indications and usage

Tolterodine is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. It is available as 1 and 2mg tablets for twice daily and 4mg extended release tablets for once daily administration orally.[79]

Contraindications

Tolterodine is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who have demonstrated hypersensitivity to the drug or its ingredients.[80]

Precautions

Tolterodine should be administered with caution to patients with

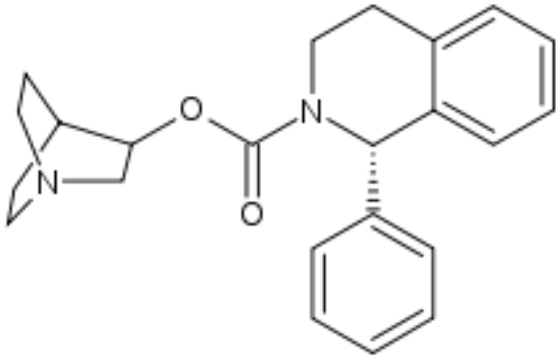
a) Clinically significant bladder outflow obstruction because of the risk of urinary retention
b) Patients with gastrointestinal obstructive disorders such as pyloric stenosis because of the risk of gastric retention
c) Controlled Narrow-Angle Glaucoma
d) Reduced Hepatic and Renal Function
e) Myasthenia Gravis
f) Patients with Congenital or Acquired QT Prolongation.[80]

Drug-Drug Interactions

Fluoxetine is a selective serotonin reuptake inhibitor and a potent inhibitor of CYP2D6 activity therefore it significantly inhibits the metabolism of tolterodine resulting in a 4.8-fold increase in plasma levels of tolterodine.[81]

CYP3A4 inhibitors like azole antifungals (e.g., ketoconazole, itraconazole), macrolide antibiotics (e.g., erythromycin, clarithromycin), cyclosporine or vinblastine significantly increases plasma concentrations of tolterodine when co administered to subjects who are poor metabolisers.[77]

SOLIFENACIN



Chemistry

Solifenacin succinate is a bladder-selective, muscarinic (M_1 and M_3) receptor antagonist. Chemically solifenacin succinate is butanedioic acid and is compounded with (1S)-(3R)-1-azabicyclo[2.2.2]oct-3-yl 3,4-dihydro-1-phenyl-2(1H)-iso -quinolinecarboxylate (1:1) having an empirical formula of C23H26N2O2•C4H6O4 and a molecular weight of 480.55. Solifenacin succinate is a white to pale-yellowish-white crystal or crystalline powder which is freely soluble at room temperature in water, glacial acetic acid, dimethyl sulfoxide and methanol. [82, 83]

In drug development solifenacin has been shown to have functional selectivity for the bladder over other organs in animal models. In vivo and in vitro studies have shown greater bladder selectivity over salivary gland tissue than tolterodine and oxybutynin. This relative bladder selectivity was the rationale for development of solifenacin in the treatment of OAB.[84]

Mechanism of action

Normally binding of acetylcholine to muscarinic receptors, particularly the M_3 receptor subtype plays a critical role in the contraction of smooth muscle. Solifenacin prevents the binding of acetylcholine to these receptors and reduces smooth muscle tone in the bladder, allowing the bladder to retain larger volumes of urine and thereby reducing the number of micturition, urgency and incontinence episodes.

Because of a long elimination half life, a once-a-day dose can offer 24 hour control of the urinary bladder smooth muscle tone.[85]Although solifenacin acts at muscarinic receptors that affect both bladder (M_1) and salivary gland (M_3) function, the drug demonstrates selectivity for the bladder over the salivary gland in vitro. The inhibition by solifenacin of the carbachol-evoked increases in intracellular calcium levels (indicative of muscarinic receptor inhibition) in bladder smooth muscle cells was 3.6-fold greater than that in the corresponding salivary gland cells. This suggests the potential for solifenacin to be less associated with dry mouth than the other antimuscarinic agents.[84]

Pharmacokinetics

Absorption:

After oral administration of Solifenacin succinate, peak plasma levels (Cmax) are reached within 3 to 8 hours and steady state ranges from 32.3 to 62.9 ng/mL for 5 and 10 mg tablets, respectively. Solifenacin has 90% bioavailability and a long half-life of 45–68 hours. The Cmax, AUC and t1/2 values were 20-25% higher in elderly patients (65 to 80 years) as compared to the younger patients (18 to 55 years). There is no significant effect of food on the pharmacokinetics of solifenacin.[86]

Distribution:

Solifenacin is approximately 98% bound to human plasma proteins, principally to α1-acid glycoprotein. It is highly distributed to non-CNS tissues having a mean steady state volume of distribution of 600L.[87]

Metabolism:

Solifenacin is extensively metabolised in the liver. It is primarily metabolised by CYP3A4. The primary metabolic routes of solifenacin are through N-oxidation of the quinuclidin ring and 4R-hydroxylation of tetrahydroisoquinoline ring.

Metabolism gives rise to one pharmacologically active metabolite (4R-hydroxy solifenacin) occurring at low concentrations which is unlikely to contribute significantly to clinical activity and three pharmacologically inactive metabolites (N-glucuronide and the N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been found in human plasma after oral dosing.[82]

Excretion

Solifenacin is eliminated 69.2% in the urine and 22.5% in the faeces. The major metabolites identified in urine were N-oxide of solifenacin, 4R-hydroxy solifenacin and 4R-hydroxy- N-oxide of solifenacin and in faeces 4R-hydroxy solifenacin.

The pharmacokinetics of solifenacin is not significantly influenced by age, gender and has not been established yet in pregnant, lactating mothers and paediatric patients.[87]

Adverse effects

The most common anticholinergic side effects of solifenacin are dry mouth, blurred vision, urinary retention and constipation. Others include peripheral oedema, hypersensitivity reactions, rash, pruritus and urticaria. Angioedema of the face, lips, tongue and larynx have been reported with solifenacin. Angioedema associated with upper airway swelling may be life threatening and in such cases solifenacin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be provided. CNS side effects include headache, confusion and hallucinations. QT prolongation has also been reported rarely.[88]

Indications and usage

Solifenacin succinate is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency. Available as 5mg and 10mg tablets once daily for oral administration.[89]

Contraindications

Solifenacin succinate is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma and in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.[82]

Precautions

Solifenacin succinate like other anticholinergic drugs, should be administered with caution to patients with

a) Clinically significant bladder outflow obstruction because of the risk of urinary retention
b) Gastrointestinal Obstructive Disorders and Decreased GI Motility
c) Controlled Narrow-Angle Glaucoma
d) Reduced Renal Function- In patients with severe renal impairment i.e. creatinine clearence less than 30mL/min there is a 2.1-fold increase in AUC and 1.6-fold increase in half life of solifenacin.
e) Reduced Hepatic Function- dose greater than 5 mg are not recommended in patients with moderate to severe hepatic impairment as it causes a 2-fold increase in the t1/2 and 35% increase in AUC of the drug
f) In patients with Congenital or Acquired QT Prolongation.[82]
g) In combination with drugs which either inhibit or induce CYP3A4 enzyme. Exposure to solifenacin succinate may be increased by drugs that inhibit the cytochrome P450 isoenzyme CYP3A4 i.e. ketoconazole or ritonavir. Therefore dose reduction must be considered.[90]

MATERIALS AND METHODS

A prospective study was conducted from 01-12-2008 to 31-05-2010 on patients with Overactive Bladder Syndrome presenting to Department of Urology.

SOURCE OF DATA (SAMPLE):

Patients presenting to the Department of Urology at R.L.Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar with clinical diagnosis of Overactive Bladder.

DATA COLLECTION:

A proforma containing detailed information on each patient was prepared according to the protocol designed for the study. Informed consent was taken from all the patients included in the study. Ethical clearance was obtained from the institutional ethics committee.

INCLUSION CRITERIA:

1. Patients of either sex.
2. Patients above the age of 18years
3. Patients with Overactive Bladder symptoms in conditions including
    - Idiopathic Detrusor overactivity.
    - Neurogenic Detrusor overactivity- Stroke, Parkinson's disease, brain injury and trauma, spinal cord lesions, Multiple sclerosis, Diabetes mellitus etc.
    - Non- Neurogenic Detrusor overactivity- Bladder infection, Bladder outlet obstruction (Pelvic organ prolapse), Bladder tumor, stones and Post Hysterectomy.
    - Aging.

EXCLUSION CRITERIA:

1. Patients with occult vesico-vaginal fistula or uretero-vaginal fistula.
2. Pregnant mothers.
3. Patients with Glaucoma.
4. Pure stress incontinence.

A total of 60 patients with Overactive Bladder were enrolled in the study. They were randomized into 2 groups of 30 each to receive either Tab. Tolterodine 4mg (TORQ SR, Reddy's Laboratory) or Tab. Solifenacin 5mg (SOLITEN, Ranbaxy laboratories) orally once daily.

Relevant data were taken from the patients. The data included hospital number, name, age & sex of the patient, date of visiting OPD and history of presenting illness. The proforma also enlisted general physical examination, vital signs and systemic examination. Patients were followed up at 2, 4 & 8 weeks and assessed for the efficacy and safety of the both the treatments.

Post void residual volume of urine was measured using ultrasonography at baseline and 8 weeks to assess the bladder function. Assessment of Symptoms was done using OAB Symptom Composite Score (OAB-SCS).[91] It is an objective scoring system that comprises of common patient-reported diary data, including

- 24-hour voiding frequency
- Urgency severity associated with each toilet void
- Frequency of UUI episodes.

The Urgency Severity is determined by a 5-point scale (OAB-SCS Points)

None,No urgency	Mild, Aware easily tolerable	Moderate, Interferes with usual tasks	Severe, Extreme urge,abruptly stops tasks or activities	UUI episode not associated with toilet void
1	2	3	4	5

The patients were advised to maintain a voiding diary and were asked to record the 24hr voiding frequency, urgency severity per void and episodes of urge incontinence (UUI).

The OAB-SCS is calculated as follows:

OAB-SCS = OAB-SCS Points /voiding Event × No. of voiding Events (in 24hrs).

Quality of life was assessed using Patient Global Impression on Improvement (PGI-I) scale.[92] This validated questionnaire measures a subject's self perceived change in his/her condition with treatment. It includes a psychiatric stem and a lower urinary tract stem.

Psychiatric Stem :

(Overall improvement)

1. Very much better
2. Much better
3. A little better
4. No change
5. A little worse
6. Much worse
7. Very much worse

Lower Urinary Tract Stem :

(Urinary symptoms)

1. Very much better
2. Much better
3. A little better
4. No change
5. A little worse
6. Much worse
7. Very much worse

A reduction in OAB- SCS and PGI-I scores between and within the groups was analysed. Adverse effects of both the drugs were recorded and patients were asked to report occurrence of any adverse effect at any time during the study period.

Lab Investigations included RBS, urine analysis, ultrasound examination of bladder and prostate, X-ray KUB and urodynamic evaluation as and when required.

Data were analysed descriptively. Efficacy of the treatments in reducing post void residual volume within and between the groups was analysed by paired and unpaired-T test respectively. Wilcoxon sign ranks test and Mann Whitney U test was applied to compare mean OAB-SCS and PGI-I scores within and between the groups respectively. A P value of < 0.05 was considered significant.

RESULTS

TABLE 1: AGE DISTRIBUTION

Age in years	Tolterodine		Solifenacin	
	No.	%	No.	%
20-39	7	23.3	9	30
40-59	7	23.3	6	20
60-79	15	50	11	36.7
>80	1	3.4	4	13.3
Total	30	100	30	100
Mean ± SD	55.5 ± 17.7		54.93 ± 21.6	

Majority of the patients in both the groups were between 60 – 79 years. The mean age ± SD was 55.5 ± 17.7 and 54.93 ± 21.6 in the Tolterodine and Solifenacin group respectively and there was no relevant statistical difference between the groups.

TABLE 2: GENDER WISE DISTRIBUTION OF PATIENTS

Gender	Tolterodine		Solifenacin	
	No.	%	No.	%
Male	20	66.7	19	63.3
Female	10	33.3	11	36.7
Total	30	100	30	100

The gender wise distribution was comparable for both the groups. Male patients were predominant in both the groups.

ASSOCIATED ILLNESS

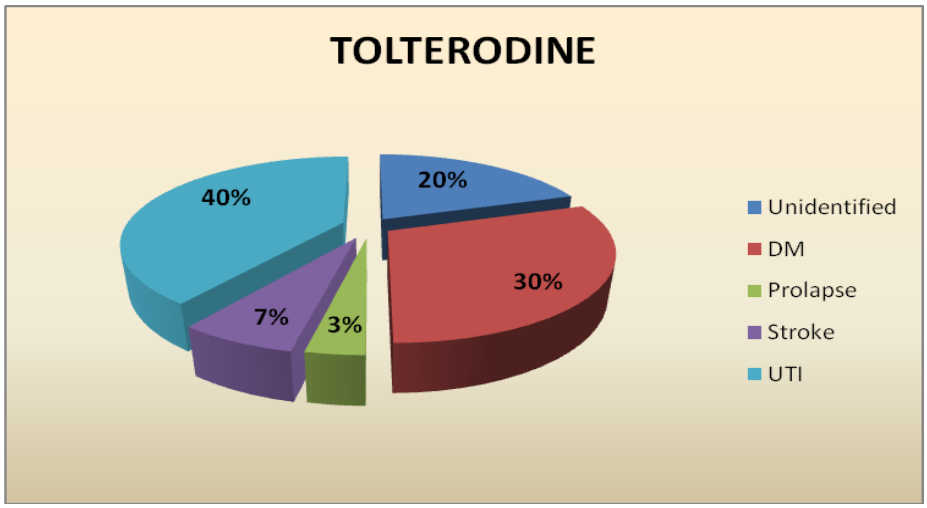


FIGURE 5

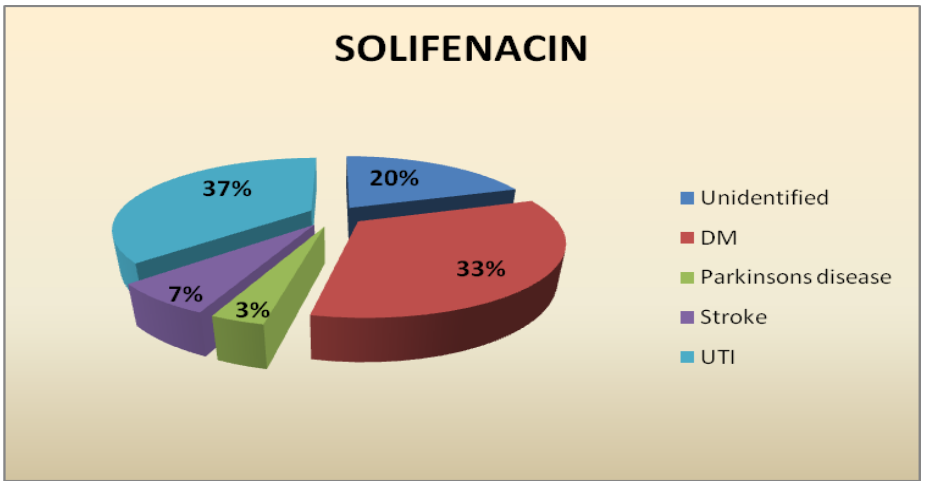
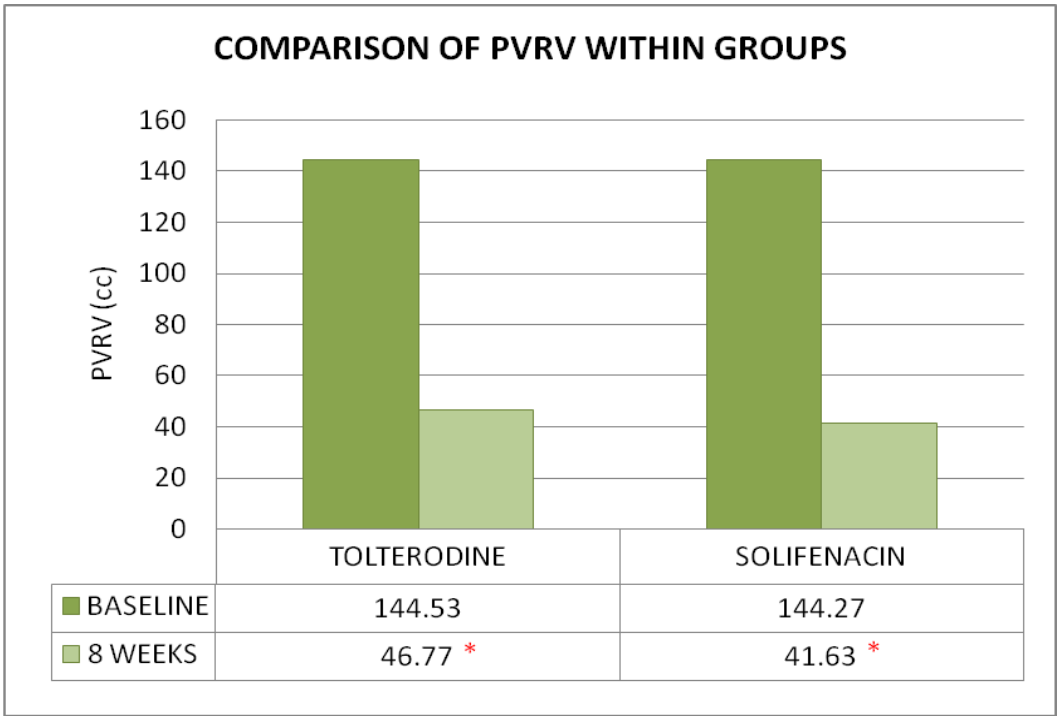


FIGURE 6

The prevalence of associated illnesses was similar in both the treatment groups. Urinary tract infection was commonest with 12 (40%) and 11 (37%) followed by diabetes 9 (30%) and 10 (33%) and stroke 2 (7%) and 2 (7%) in the Tolterodine and Solifenacin groups respectively. There was 1(3%) case of Pelvic organ prolapse in Tolterodine group and 1(3%) case of Parkinson's disease in Solifenacin group.



* P < 0.05 is significant

FIGURE 7

Figure 7 shows the comparison of Post void residual volume of urine within the treatment groups. There was significant reduction in PVRV at 8 weeks compared to baseline in both Tolterodine and Solifenacin group with a P-value of 0.001 and 0.005 respectively.

TABLE 3: COMPARISON OF PVRV BETWEEN GROUPS

Time interval	**Tolterodine**		**Solifenacin**		**P-value**
	Mean	S.D	Mean	S.D	
Baseline (cc)	144.53	47.72	144.27	51.01	0.644
8 weeks (cc)	46.77	21.96	41.63	13.85	0.065

Table 3 shows the comparison of PVRV between the treatment groups. There was a greater reduction in PVRV from baseline in the Solifenacin group (71.14%) compared to Tolterodine group (67.6%), but it was not found to be statistically significant.

TABLE 4: REDUCTION IN OAB-SCS SCORES WITHIN GROUP

Time interval	Tolterodine			Solifenacin		
	Mean	% change from baseline	P-value	Mean	% change from baseline	P-value
Baseline	42.6	----	----	42.8	----	----
2 weeks	19.7	53.7%	<0.001*	16.0	62.6%	<0.001*
4 weeks	11.3	73.4%	<0.001*	10.6	75.2%	<0.001*
8 weeks	9.6	77.4%	<0.001*	9.4	78%	<0.001*

* P < 0.05 is significant

Table 4 shows the mean OAB-SCS scores and percentage change from baseline at 2, 4 & 8 weeks within the treatment groups. There was significant reduction in OAB-SCS scores at each follow up visits in both the groups with a P-value of < 0.001.

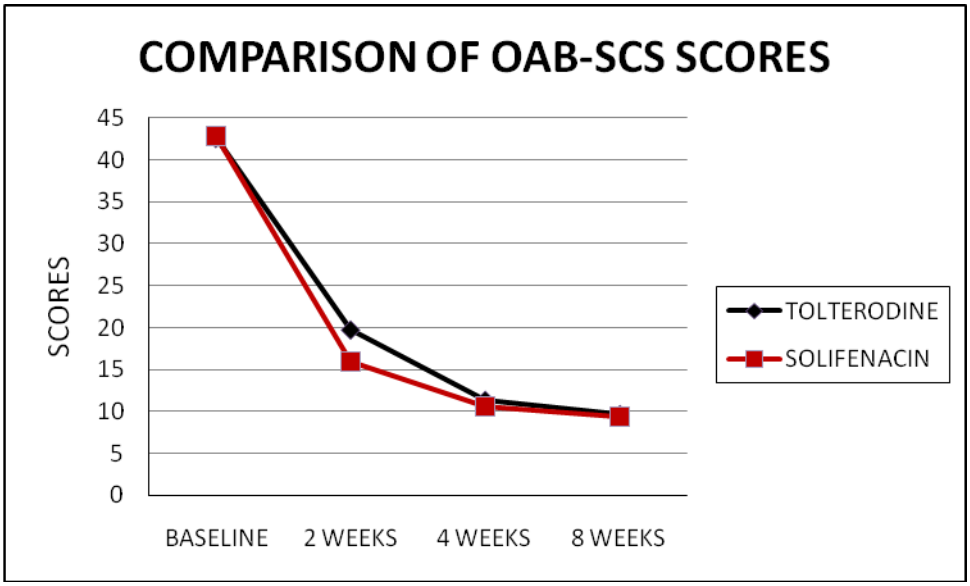


FIGURE 8

TABLE 5: COMPARISON OF OAB-SCS SCORES BETWEEN GROUPS

Time interval	Tolterodine		Solifenacin		P-value
	Mean	S.D	Mean	S.D	
Baseline	42.6	5.86	42.8	4.82	0.888
2 weeks	19.7	3.41	16.0	4.41	0.001*
4 weeks	11.3	2.43	10.6	1.98	0.332
8 weeks	9.6	1.98	9.4	1.03	0.495

* $P < 0.05$ is significant

Figure 8 and Table 5 shows the comparison of OAB-SCS scores between Tolterodine and Solifenacin group at each follow up visit. There was significant reduction in OAB-SCS scores in the Solifenacin group at 2nd week of follow up visit (P-value = 0.001) compared to Tolterodine group.

TABLE 6: REDUCTION IN PGII- PS SCORES WITHIN THE GROUPS

Time interval	Tolterodine			Solifenacin		
	Mean	% change from baseline	P-value	Mean	% change from baseline	P-value
Baseline	6.47	----	----	6.40	----	----
2 weeks	3.73	42.34%	<0.001*	2.77	56.7%	<0.001*
4 weeks	1.80	72.2%	<0.001*	1.50	76.6%	<0.001*
8 weeks	1.37	78.8%	<0.001*	1.30	79.7%	<0.001*

* P < 0.05 is significant

Table 6 shows the mean PGII-PS scores and percentage change from baseline at 2, 4 & 8 weeks within the treatment groups. There was significant reduction in PGII-PS scores at each follow up visits in both the groups with a P-value of < 0.001

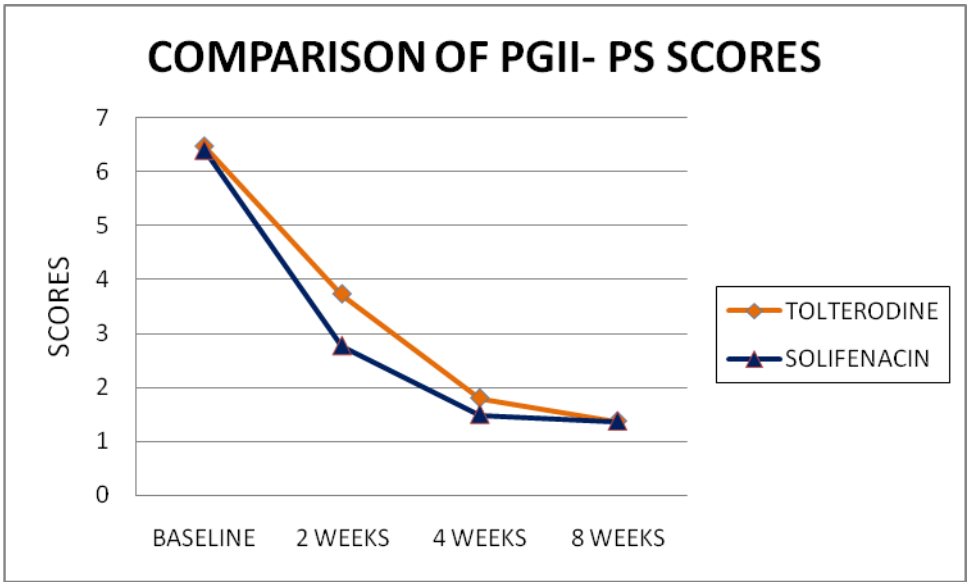


FIGURE 9

TABLE 7: COMPARISON OF PGII- PS SCORES BETWEEN GROUPS

Time interval	Tolterodine		Solifenacin		P-value
	Mean	S.D	Mean	S.D	
Baseline	6.47	0.68	6.40	0.72	0.740
2 weeks	3.73	1.08	2.77	0.97	0.001*
4 weeks	1.80	0.76	1.50	0.57	0.130
8 weeks	1.37	0.62	1.37	0.49	0.733

* $P < 0.05$ is significant

Figure 9 and Table 7 shows the comparison of PGII-PS scores between Tolterodine and Solifenacin group at each follow up visit. There was significant reduction in PGII-PS scores in the Solifenacin group at 2nd week of follow up visit (P-value = 0.001) compared to Tolterodine group.

TABLE 8: REDUCTION IN PGII- LUTS SCORES WITHIN THE GROUPS

Time interval	Tolterodine			Solifenacin		
	Mean	% change from baseline	P-value	Mean	% change from baseline	P-value
Baseline	6.50	----	----	6.53	----	----
2 weeks	4.07	37.4%	<0.001*	3.50	46.4%	<0.001*
4 weeks	1.87	71.23%	<0.001*	1.60	75.5%	<0.001*
8 weeks	1.47	77.4%	<0.001*	1.37	79%	<0.001*

* P < 0.05 is significant

Table 8 shows the mean PGII-LUTS scores and percentage change from baseline at 2, 4 & 8 weeks within the treatment groups. There was significant reduction in PGII-LUTS scores at each follow up visits in both the groups with a P-value of < 0.001

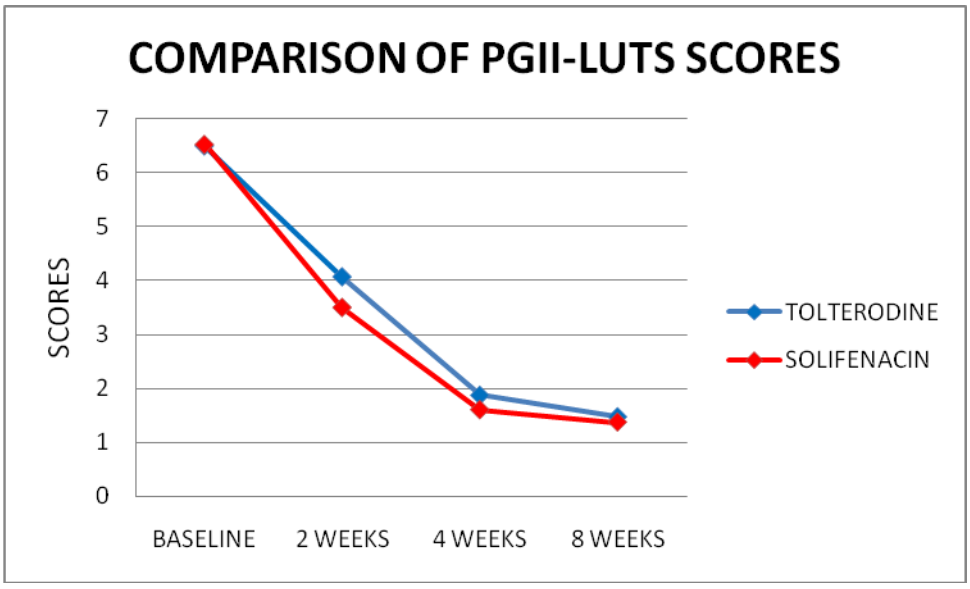


FIGURE 10

TABLE 9: COMPARISON OF PGII- LUTS SCORES BETWEEN GROUPS

Time interval	Tolterodine		Solifenacin		P-value
	Mean	S.D	Mean	S.D	
Baseline	6.50	0.68	6.53	0.63	0.919
2 weeks	4.07	0.94	3.50	1.04	0.039*
4 weeks	1.87	0.73	1.60	0.62	0.154
8 weeks	1.47	0.68	1.37	0.49	0.773

* $P < 0.05$ is significant

Figure 10 and Table 9 shows the comparison of PGII-LUTS scores between Tolterodine and Solifenacin group at each follow up visit. There was significant reduction in PGII-LUTS scores in the Solifenacin group at 2nd week of follow up visit (P-value = 0.039) compared to Tolterodine group.

TABLE 10: COMPARISON OF ADVERSE EFFECTS

Adverse effects	Tolterodine	Solifenacin
Dry mouth	5 (16.7%)	4 (13.33%)
Constipation	1 (3.33%)	2 (6.67%)
Blurring of vision	0	0
Tachycardia	0	0
TOTAL	6 (20%)	6 (20%)

Table 10 shows the adverse effects in both treatment groups. The most common adverse effect reported was dry mouth ie 5(16.7%) in Tolterodine group and 4(13.33%) in Solifenacin group. All the adverse effects were mild in nature and involved 6 (20%) patients in both the groups.

DISCUSSION

Urgency is the cornerstone symptom of OAB and is generally regarded as the driver for other urological symptoms and is difficult to determine owing to the attached stigma, which may prevent patients from seeking medical care. Patients who consult a doctor often do so against the background of having to overcome embarrassment and loss of dignity and it is essential that they are offered effective treatment.

The most common treatment options are conservative management (bladder training and pelvic floor muscle exercises) and pharmacological treatment. Conservative management is effective but it requires high motivation in patients. Surgical interventions are rarely done in very severe cases of OAB with reduced bladder capacity.

First-line drug treatment is usually with antimuscarinic agents. These inhibit muscarinic receptors in the urinary bladder wall, leading to a decrease in involuntary detrusor contractions and an increase in bladder capacity. However, these agents also have anticholinergic side-effects, particularly dry mouth. Therefore achieving an optimum balance between efficacy and tolerability in individual patients is a key factor in helping to achieve persistence with treatment. Tolterodine is a widely used antimuscarinic agent in the treatment of Overactive bladder. Solifenacin is a newer antimuscarinic agent that shows apparent functional selectivity for bladder over other organs. [5]

In the present study, we have compared the efficacy and safety of oral Tolterodine 4mg once daily with oral Solifenacin 5mg once daily in the treatment of Overactive bladder. The parameters assessed were post void residual volume of urine, symptomatic improvement using Overactive Bladder Symptom composite score (OAB-SCS) and quality of life using PGI-I questionnaire.

The prevalence of OAB increases with age.[11] In our study, the mean age of the patients in Tolterodine group was 55.5 ± 17.7 years, while that of Solifenacin group was 54.93 ± 21.6 years. In both the groups majority of patients were more than 60years.

The incidence of OAB is almost similar or slightly higher in females.[10] In our study there were 66.7% males and 33.3% females in Tolterodine group and 63.3% males and 36.7% females in Solifenacin group. In Solifenacin (flexible dosing with 5 mg and 10 mg doses) OD and Tolterodine ER 4 mg OD as an Active comparator in a Randomised (STAR) trial 85.3% of patients enrolled in the study were females.[88] The lower incidence of females in our study could be due to poor reporting of women to the health care provider in rural population.

Urinary tract infection was commonest associated illness in our study followed by diabetes, and stroke .There was one case of Pelvic organ prolapse in Tolterodine group and one case of Parkinson's disease in Solifenacin group.

There are only a few comparative studies of Solifenacin and Tolterodine conducted till date. The studies by Chapple et al 2004 and 2005, have shown that Solifenacin (5mg and 10mg) was non inferior to Tolterodine (4mg) for the reduction in frequency of voids and had greater efficacy than the comparator for all other outcomes that assess the symptoms and quality of life of OAB patients.[5, 88]

In the present study, there was statistically significant reduction in post void residual volume (PVRV) of urine from baseline in both the treatment groups. Although Solifenacin produced a greater reduction in PVRV compared to Tolterodine, the difference was not statistically significant.

These results were in accordance with the results of other studies where in antimuscarinic agents have shown to improve the functional bladder capacity, increase the volume voided and reduce the PVRV of urine.[5, 88]

Over-Active Bladder-Symptom Composite Score (OAB-SCS) was used in this study as a single quantifiable value to overall number and severity of OAB symptoms. It has been used in several studies involving other antimuscarinic agents and has been shown to be a validated objective scoring system for OAB symptoms.[91] Both Solifenacin and Tolterodine showed a significant reduction in OAB-SCS scores at 2,4 and 8 weeks ($P<0.001$) compared to baseline. Although Solifenacin showed a greater percentage of reduction in scores compared to Tolterodine at each follow up visit, the difference was statistically significant only at 2 weeks. ($P=0.001$)

In studies by Chapple et al 2005 and Cardozo et al 2008, Solifenacin has shown to improve the Quality of life significantly compared to Tolterodine and placebo respectively from 4 weeks of the treatment period. [88,89] In our study there was significant improvement in quality of life with both the treatment groups as assessed be the psychiatric and lower urinary tract stem of the PGI-I scale at 2, 4 and 8 weeks. In accordance with other studies Solifenacin showed better improvement in the Quality of life compared to Tolterodine, but the difference was statistically significant only at 2 weeks.($P<0.05$)

In the current study both the study drugs were well tolerated and side effects were mild in nature. Dry mouth was the most common side effect observed in both the groups. The incidence of dry mouth in patients treated with Solifenacin was 13.33% as compared to 16.7% with Tolterodine. Constipation was observed more with Solifenacin (6.67%) than Tolterodine (3.33%). In previous studies dry mouth was observed more with Solifenacin which is in contrast to this study but incidence of constipation was comparable to our study.[5]

CONCLUSION

The results of the present study show that administration of Solifenacin 5 mg once daily is an effective and well tolerated new therapy for treating symptomatic OAB. Treatment with Solifenacin effectively reduced urgency with a consequent increase in functional bladder capacity associated with reduced frequency, incontinence and increased volume voided similar to Tolterodine. Furthermore, Solifenacin has also shown to produce faster improvement in OAB symptoms and the quality of life of OAB sufferers within 2 weeks of treatment compared to Tolterodine. In addition patients treated with Solifenacin showed a lower incidence of anticholinergic side-effects, particularly dry mouth, suggesting relative selectivity of Solifenacin for bladder over salivary gland. This ensures better patient compliance and makes Solifenacin an excellent choice for the management of overactive bladder.

SUMMARY

The aim of the study was to evaluate the efficacy and safety of Solifenacin compared to Tolterodine in the management of overactive bladder.

A prospective study was conducted on 60 patients of whom 30 patients were assigned to Tab Tolterodine 4mg once a day and the other 30 patients received Tab Solifenacin 5 mg once a day. The study drugs were given to the patients for a period of 8 weeks.

Majority of the patients in the study were males. A greater number of patients were above 60 years of age, with the mean age being 55.5 ± 17.7 years in the Tolterodine group and 54.93 ± 21.6 years in the Solifenacin group. Majority of the patients had associated urinary tract infection in both groups followed by Diabetes which was the next commonest associated illness.

A comparison of PVRV showed a significant reduction in residual volume with Solifenacin which was similar to Tolterodine. When OAB-SCS and PGI-I scores were compared, both the treatments showed significant reduction in OAB symptoms and improvement in quality of life within the groups at every follow up visit. Solifenacin produced a greater reduction in OAB-SCS and PGI-I scores compared to Tolterodine at all follow up visits but the reduction was statistically significant only at 2 week.

Adverse events were infrequent and mild in nature. Dry mouth and constipation were reported which did not warrant discontinuation and withdrawal from the study.

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PROFORMA

Name- IP/OP No.-
Age- Address-
Sex-
History-

Associated illness-
Date of start of treatment-

PHYSICAL EXAMINATION

General Examination:

Systemic Examination: -CVS :
-RS :
-P/A :
-CNS :

INVESTIGATIONS

1) RBS : 2) Urine analysis :

3) USG: Post void Residual volume (PVRV) 3) Others :

Baseline	8weeks

OVERACTIVE BLADDER SYMPTOM COMPOSITE SCORE (OAB-SCS)

OAB-SCS 5-POINT SCALE	OAB-SCS POINTS x NO. OF EVENTS			
	Base line	2 weeks	4 weeks	8 weeks
1				
2				
3				
4				
5				
Total score				

PATIENT GLOBAL IMPRESSION ON IMPROVEMENT SCALE

Psychiatric Stem :	**Lower Urinary Tract Stem :**
(Overall improvement)	(Urinary symptom)
8. Very much better	1. Very much better
9. Much better	2. Much better
10. A little better	3. A little better
11. No change	4. No change
12. A little worse	5. A little worse
13. Much worse	6. Much worse
14. Very much worse	7. Very much worse
• Baseline :	Baseline :
• 2 Weeks :	2 Weeks :
• 4 Weeks :	4 Weeks :
• 8 Weeks :	8 Weeks :

ADVERSE EFFECTS

1. Dry mouth – mild: moderate: severe:
2. Blurring of vision – mild: moderate: severe:
3. Tachycardia – Rate : /min
4. Constipation – (No. of times per week)
5. Glaucoma

KEY TO MASTER CHART

Sl.No – Serial Number

Hosp No. – Hospital number

M – Male

F – Female

DM – Diabetes Mellitus

UTI – Urinary tract infection

PD – Parkinsons disease

PVRV – Post void residual volume of urine

OAB-SCS – Overactive Bladder Symptom composite score

PGII-PS – Patient global impression on improvement- Psychiatric Stem

PGII-LUTS – Patient global impression on improvement- Lower urinary tract stem

ADE – Adverse effect

Dm – Dry mouth

C - Constipation

Introduction

Aims and Objectives

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Results

Discussion

Summary

Conclusion

Bibliography

Annexures

MASTER CHART : TOLTERODINE

Sl no.	PATIENT DETAILS				PVRV (cc)		BASELINE			2 WEEKS			4 WEEKS			8 WEEKS			ADE
	Hosp No.	Age (yrs)	Sex	Ass Illness	Base line	8 wks	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	
1	469218	70	M	DM	150	30	45	6	7	21	3	4	11	1	2	8	1	2	Dm
2	256711	75	M	Stroke	113	28	47	7	7	25	3	3	9	1	1	9	1	1	
3	467853	60	M	UTI	143	34	45	5	6	18	4	4	11	2	2	11	2	2	
4	402753	49	F	DM	136	34	36	6	7	20	3	3	10	2	2	9	2	2	
5	451317	38	M	UTI	113	45	48	7	7	19	5	5	16	3	3	15	3	3	Dm
6	564375	70	M	DM	220	60	48	6	6	21	3	3	11	2	2	9	1	1	
7	537765	76	M	DM,UTI	228	110	50	5	5	25	5	5	14	3	3	10	1	1	
8	543036	60	M	Stroke	98	32	48	6	7	27	5	5	16	3	3	15	3	3	C
9	280159	35	F	UTI	99	30	40	7	6	18	5	5	10	2	2	8	1	1	
10	308299	75	M	UTI,	132	33	51	7	7	20	4	4	11	1	1	9	1	1	
11	451266	60	M	UTI	169	54	35	7	7	13	5	5	11	2	2	10	1	1	
12	525620	70	F	DM	120	87	45	7	6	19	3	3	11	1	1	8	1	1	Dm
13	532153	55	F	UTI	96	43	43	6	5	17	2	2	10	1	1	8	1	1	
14	571069	55	F		224	31	48	7	7	20	5	5	17	3	3	14	1	1	
15	568765	70	M	DM	176	46	45	7	7	21	3	3	11	1	1	9	1	1	

MASTER CHART : TOLTERODINE

Sl no.	PATIENT DETAILS				PVRV (cc)		BASELINE			2 WEEKS			4 WEEKS			8 WEEKS			ADE
	Hosp No.	Age (yrs)	Sex	Ass Illness	Base line	8 wks	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	
16	571825	85	M		223	37	50	7	7	21	3	3	10	1	1	9	1	1	
17	546930	32	F	UTI	87	30	43	6	6	19	4	4	9	2	2	9	1	1	
18	544987	50	M		178	80	32	6	5	24	2	3	11	1	1	8	1	1	
19	545673	26	F	UTI	144	56	30	7	7	15	5	5	15	3	3	10	2	2	
20	478564	57	M		209	100	47	7	7	26	5	5	16	2	2	9	1	1	
21	500987	54	M	DM	134	40	44	7	7	20	5	5	12	2	2	10	1	1	Dm
22	487776	60	F	Prolapse	189	60	37	6	6	18	3	4	11	1	1	11	1	1	
23	567543	23	F	UTI	76	28	45	7	7	15	3	3	10	1	1	7	1	1	
24	543298	21	F	UTI	56	29	34	6	6	16	2	4	10	1	1	8	1	1	
25	498723	72	M		100	30	48	7	7	20	3	3	11	2	2	9	2	2	
26	601131	68	M	UTI	156	35	43	7	7	22	5	5	10	2	2	10	1	1	Dm
27	600502	70	M	DM	146	45	42	7	7	21	3	5	8	1	2	8	2	2	
28	255485	42	M		156	53	36	6	6	18	3	5	9	2	2	9	2	2	
29	598915	60	M	DM	178	56	39	7	7	19	5	5	10	3	3	10	1	3	
30	598991	27	M	UTI	87	27	35	5	6	14	3	4	8	2	2	8	2	2	

MASTER CHART: SOLIFENACIN

Sl no.	PATIENT DETAILS				PVRV (cc)		BASELINE			2 WEEKS			4 WEEKS			8 WEEKS			ADE
	Hosp No.	Age (yrs)	Sex	Ass Illness	Base line	8 wks	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	
1	478767	56	M	PD	156	55	40	7	7	15	2	2	11	2	2	10	1	1	
2	303466	70	M	DM	220	75	46	6	6	14	4	5	11	2	2	9	2	2	
3	528950	28	M	UTI	100	35	50	5	5	10	3	4	9	1	1	9	1	1	
4	544069	75	M	Stroke	140	55	33	7	7	11	2	3	10	1	1	10	1	1	
5	507291	82	M	UTI	210	40	48	7	7	20	3	3	14	2	2	11	2	2	Dm
6	597858	55	F		156	53	36	6	6	18	5	5	14	2	2	9	2	2	
7	596055	75	M	DM	160	35	44	7	7	17	3	4	11	1	1	9	1	1	
8	534618	70	M		240	54	47	7	7	14	2	3	11	2	2	11	1	1	C
9	548620	65	M		80	30	44	7	7	18	3	3	13	2	2	10	1	1	
10	565934	85	M	DM,UTI	180	43	37	6	6	24	4	5	14	3	3	11	2	2	
11	495412	63	M	UTI	240	50	45	7	7	24	4	5	15	2	3	9	2	2	
12	571826	72	M		97	44	45	7	7	14	3	4	10	1	1	8	1	1	
13	499678	70	M	DM	135	30	43	6	7	16	2	3	8	1	1	8	1	1	
14	548157	21	F	UTI	78	31	50	5	6	14	1	1	7	1	1	7	1	1	
15	548155	47	F	DM	87	30	34	6	6	11	2	3	10	2	2	10	2	2	Dm

MASTER CHART: SOLIFENACIN

Sl no.	PATIENT DETAILS				PVRV (cc)		BASELINE			2 WEEKS			4 WEEKS			8 WEEKS			ADE
	Hosp No.	Age (yrs)	Sex	Ass Illness	Base line	8 wks	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	OAB-SCS	PGII-PS	PGII-LUTS	
16	548154	80	M	Stroke	134	80	45	7	7	13	2	3	8	1	1	9	1	1	
17	543534	30	M	UTI	189	60	39	7	7	23	3	4	11	2	2	10	2	2	C
18	535657	21	F	UTI	76	28	42	5	5	11	1	2	11	1	1	9	1	1	
19	550743	30	F	UTI	56	29	45	6	6	16	3	4	9	1	1	9	1	1	
20	595243	45	F		100	30	43	7	7	13	2	3	8	1	1	8	1	1	
21	469868	80	M	DM	143	45	46	7	7	22	3	4	12	2	2	10	2	2	
22	597153	28	M	UTI	98	43	47	5	7	18	3	4	11	1	2	11	1	1	
23	564709	55	F	DM	143	31	38	6	6	13	3	5	8	1	1	8	1	1	Dm
24	525369	76	M	DM	156	45	45	6	6	21	2	3	10	1	2	9	1	1	
25	592721	27	F	UTI	200	45	49	7	7	20	3	3	10	1	1	9	1	1	
26	593142	30	F		178	36	34	7	7	15	3	3	11	2	2	9	2	2	
27	536497	76	F	DM	196	32	46	7	7	11	2	2	9	1	1	9	1	1	Dm
28	592759	54	F		113	24	37	7	7	12	3	4	10	2	2	10	2	2	
29	536497	20	M	UTI	100	30	42	6	6	10	2	3	10	2	2	10	2	2	
30	550554	62	M	DM	167	31	44	6	6	23	5	5	11	1	1	11	1	1	