A FOGSI President's Initiative

WE FOR स्त्री
Safer • Stronger • Smarter

KEY PRACTICE POINTS 2019
INDIAN PERSPECTIVE

By Dr. Nandita Palshetkar

KEY PRACTICE POINTS ON

OVERACTIVE BLADDER

science integra®

For OAB patients with

- Urgency
- Overflow
- Leakage
- Nocturia

Rx OAB-F™

Mirabegron Extended Release 25mg/50mg Tablets

First Line Management for Overactive Bladder

- Novel mechanism of action & proven efficacy across multiple RCTs
- Superior treatment adherence for OAB
- Lower incidences of adverse events as compared to antimuscarinics

Dosage

Recommended by FDA

25/50mg
Once a Day with or without food
Depending on severity of symptoms

Symptoms are controlled within 7 days[1]

ABRIDGED PRESCRIBING INFORMATION FOR OAB-F

Composition: Mirabegron (Extended Release) 25 mg and 50 mg tablets for oral use.

Indications and uses: OAB-F is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. **Dosage and Administration:** Recommended starting dose is 25 mg once daily, with or without food. 25 mg is effective within 8 weeks. Based on individual efficacy and tolerability, may increase dose to 50 mg once daily. Swallow whole with water, do not chew, divide or crush. Patients with Severe Renal Impairment or Patients with Moderate Hepatic Impairment: Maximum dose is 25 mg once daily. **Contraindication:** Hypersensitivity reactions.**Warnings and Precautions**: *Increases blood pressure*: OAB-F can increase blood pressure. Regular blood pressure evaluations recommended, especially for hypertensive patients. Not recommended for use in severe hypertension patients. *Urinary retention in Patients with Bladder Outlet Obstruction and in Patients Taking Antimuscarinic Drugs for Overactive Bladder:* Administer with caution. *Angioedema*: Angioedema of the face, lips, tongue and/or larynx has been reported with OAB-F. *Patients Taking Drugs Metabolized by CYP2D6:* Appropriate monitoring is recommended and dose adjustment may be necessary for narrow therapeutic index CYP2D6 substrates.**Adverse Reactions**: Most commonly reported adverse reactions (>2% and > placebo) were hypertension, nasopharyngitis, urinary tract infection and headache.**Use in specific population**: *Pregnancy:* Use only if the benefit to the mother outweighs the potential risk to the fetus. *Nursing Mothers*: OAB-F is not recommended for use in nursing mothers. *Paediatric population*: Safety and effectiveness of OAB-F in paediatric population has not been established. *Geriatric use*: No dosage adjustment necessary for elderly patients. *Patients with End Stage Renal Disease (ESRD) or Patients with Severe Hepatic Impairment:* Not recommended.

MARKETED BY:

Alembic Elena

Prime Corporate Park, 2nd Floor, behind ITC Grand Maratha Sheraton, Sahar Road, Andheri (E), Mumbai – 99.
Tel.: 30611698 Fax: (022) 30611682 Website: www.alembic-india.com

Dear FOGSIANs,

In this era of evidence-based medicine, Gynaecologists often must make decisions where neither evidence nor consensus exists. Fortunately, there is a growing body of evidence to assist in managing Endometriosis, Fibroids, and overactive bladder (OAB). With Key Practice Points (KPP), the idea is to regularly create evidence and consensus based practical approach to the diagnosis and management of indications, thereby ensuring a higher quality of care to patients.

The KPP from FOGSI supported in science through Science Integra will be an annual affair to bring the best talent across the country and get them to discuss, deliberate, and create easy point of reference to practice better.

Hope you all will maximise from the KPP outputs and pass on further for the betterment of the community and the STREE in all. Our sincere gratitude to Alembic Pharmaceuticals for their educational grant for the Key Practice Points.

Best wishes!

Dr. Nandita Palshetkar

MD, FCPS, FICOG
President 2019 - Federation of Obstetrics and Gynecological Societies of India (FOGSI)

KEY PRACTICE POINTS ON
OVERACTIVE BLADDER

FOGSI President : Dr. Nandita Palshetkar

Moderators : Dr. Suchitra Pandit, Dr. Alpesh Gandhi

Panelists : Dr. Seema Mehta, Dr. Madhuri Patel, Dr. Indranil Dutta, Dr. Nita Mishra, Dr. Ashwin Shetty, Dr. Rajat Mohanty, Dr. Murlidhar Pai, Dr. Sanjay Pandey, Dr. Shantha Kumari, Dr. Krishnendu Gupta, Dr. Meena Samant, Dr. Anahita Chauhan, Dr. Usha Shekhawat, Dr. Veena Acharya, Dr. Pushpa Nagar, Dr.Nita Thakre

Clinical Reporters : Dr. Swati Bhargava

From left to right: ***Standing*** – Dr. Seema Mehta, Dr. Madhuri Patel, Dr. Indranil Dutta, Dr. Nita Mishra, Dr. Ashwin Shetty, Dr. Rajat Mohanty, Dr. Suchitra Pandit, Dr. Murlidhar Pai, Dr. Alpesh Gandhi, Dr. Sanjay Pandey, Dr. Shantha Kumari, Dr. Krishnendu Gupta, Dr. Meena Samant, Dr. Anahita Chauhan, Dr. Usha Shekhawat, Dr. Veena Acharya

Sitting – Dr. Pushpa Nagar, Dr.Nita Thakre, Dr. Swati Bhargava

KEY PRACTICE POINTS
INDIAN PERSPECTIVE

Overactive bladder syndrome:
Recommendations for the assessment and management

INTRODUCTION

The International Continence Society defines overactive bladder (OAB) as a condition with characteristic symptoms of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology.[1, 2]

	EPIC[7,8]	NOBLE[6]	EpiLUTS[9]	Milsom[10]
Geography	**Canada, Germany, Italy, Sweden, UK**	**USA**	**USA**	**France, Germany, Italy, Spain, Sweden, UK**
Age of participants	≥ 18 yrs	≥ 18 yrs	≥ 40 yrs	≥ 40 yrs
Prevalence of OAB (Overall)	11.8%	16.5%	35.6%	16.6%
Prevalence in Female	12.8%	16.9%	43.1%	17.4%
Prevalence in Male	10.8%	16.0%	27.2%	15.6%

The OAB syndrome is a chronic condition that has a tremendous influence on the quality of life in both men and women. It has been reported to affect the performance of daily activities and social function such as work, traveling, physical exercise, sleep, and sexual function.[3] The prevalence of OAB in Asia is reported to be about 53.1%[4] and the prevalence seems to increase with age.[5] In the United States alone, the National Overactive Bladder Evaluation study has reported that 16.5% of study participants met the criteria for OAB, which translates to affect as many as 33 million adults.[6] The epidemiology of OAB may be an underestimation, as many patients fail to seek help due to embarrassment or ignorance. No data is available for India due to paucity of studies.

The most important symptom for the diagnosis of OAB is urgency, which is closely associated with frequent daytime desire to urinate, nocturia, and incontinence. It has been reported that nocturia is the most bothersome symptom and is directly associated with decreased sleep quality, decreased health-related quality of life (HQoL), and depression in the elderly population.[3]

Other definitions[11-13]

	Definitions
Urgency	A sudden, compelling desire to void that is difficult to defer
Urinary frequency	>8 micturitions/24 hours
Nocturia	Interruption in sleep more than two times because of need to void
Nocturnal polyuria	An excess (>20%–30%) proportion of urine excretion at night
Polyuria	>40 mL urine/kg body weight during 24 hours
Urgency urinary incontinence	Involuntary loss of urine associated with urgency
Detrusor overactivity	A urodynamic observation characterized by involuntary spontaneous or provoked detrusor contractions during the filling phase

Diagnosis of OAB is considered in the absence of urinary tract infection, metabolic disorders, or urinary stress incontinence. Only a third of OAB patients show urge incontinence also called wet OAB. This is different from incontinence due to the failure of the urethra and pelvic floor to withstand abdominal pressure that is usually not accompanied by 'urgency'. Some patients may have both OAB and urinary stress incontinence symptoms and are diagnosed as having mixed urinary symptoms.[3]

The need for the development of recommendations for OAB arose due to increasing healthcare costs, practice variations and reports of inappropriate care.

Pathophysiology

- Normal filling requires

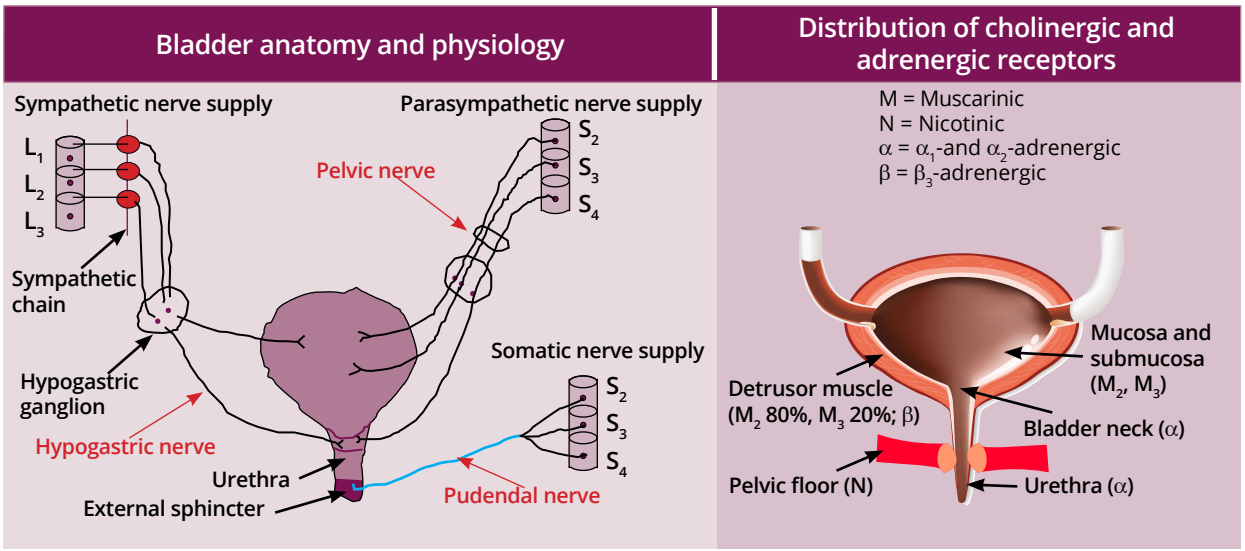
Parasympathetic inhibition and sympathetic stimulation → Reduces detrusor tone.

- Normal emptying requires

Sympathetic inhibition and parasympathetic stimulation → Increase detrusor tone.

Normal storage of urine is dependent on:

- Spinal reflex mechanism that activates sympathetic and somatic pathways to the urethral outlet



- Tonic inhibitory systems in the brain that suppress the parasympathetic excitatory outflow to the urinary bladder

Intravesical pressure lower than intraurethral pressure → Bladder filling.

Decrease in urethral resistance and contraction of detrusor muscle → Bladder emptying.

Various factors may be involved in OAB and the major cause may vary from individual to individual. Four theories have been proposed to explain the pathophysiology of OAB:

1. The neurogenic theory: Reduction in the inhibitory neural impulses and increase in the afferent impulses from the bladder trigger the voiding reflex[14]
2. The myogenic theory: The detrusor muscle becomes more sensitive to cholinergic stimulation leading to increased spontaneous activity[15]
3. The autonomous bladder theory: Alteration or exacerbation of phasic activity is generated by muscarinic stimulation[16]
4. The afferent signaling theory: Spontaneous bladder contractions during filling result in increased afferent output and hence the awareness of bladder filling[17]

All these theories attempt to explain what is referred to as 'detrusor overactivity'. The micturition reflex is activated when the detrusor muscle is stretched, while control of the bladder is achieved through a complex of interactions between the central and the peripheral nervous systems. OAB syndrome is a pathological condition that affect's the bladder's sensory pathway and contribute to the urge to urinate at a low bladder volume. The detrusor muscle is densely innervated and allows synchronous activation and a rise in bladder intra vesicle pressure. Pathological partial denervation of the detrusor may induce muscle contractions leading to an urgency sensation and possible urge of urinary incontinence. Anatomically and functionally the detrusor muscle phasic activity is also controlled by the autonomous nervous system and any imbalance in the excitation or inhibition of smooth muscle modulators may also result in detrusor overactivity.[18]

Diagnosis

Overactive bladder symptoms are usually associated with involuntary contractions of the detrusor muscle, which can result in urge incontinence, depending on the response of the sphincter.[19] The most common cause of OBS is detrusor overactivity; 64% of all patients with overactive bladder symptoms have detrusor overactivity on cystometry, and 69% of men and 44% of women with urgency have detrusor overactivity.[20]

Diagnosis

- History
- Clinical examination
- Investigations
  - » Lab investigations
  - » Imaging
    - * Ultrasound
- Urodynamic study

RECOMMENDATIONS

The risk factors to look for the diagnosis of OAB include older age, obesity, chronic constipation, and vaginal birth delivery.

What should a doctor ask?

Do you have urinary complaints

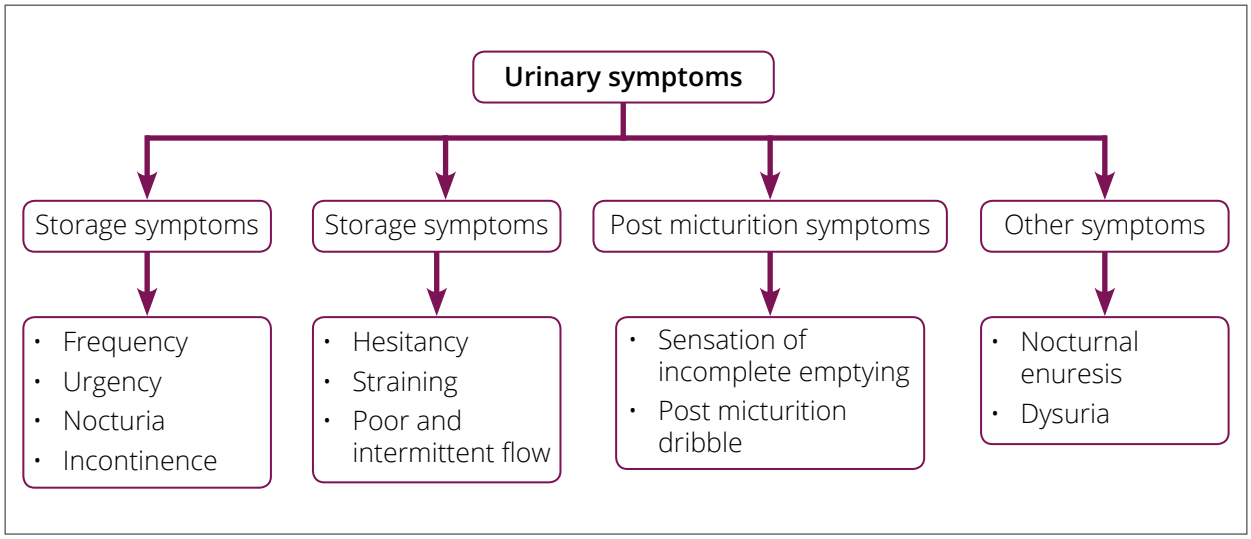
1. Frequency
2. Nocturia
3. Urgency
4. Urge incontinence
5. Stress urinary incontinence
6. Voiding difficulties
   a. Hesitancy
   b. Poor stream
   c. Incomplete voiding
   d. Post void dribble
7. Dysuria

* Gynaecologists must ask leading questions in all gynaec consultation

History

Symptom history

When urinary frequency (both daytime and night) and urgency, with or without urgency incontinence, in absence of urinary tract infection (UTI) or other obvious pathology are self reported as bothersome, the patient may be diagnosed as OAB.



Severity of symptoms can be assessed by

- Pad usage
  - » Pad weight
  - » Pad size
  - » Number of pads used
- Number of urinary incontinence episodes per day

Medical history and physical examination

Medical history[22]

- Age
- Duration
- Severity
- The degree of bother/effect on activities of daily life
- Fluid intake
- Lifestyle characteristics
- Obstetrical/gynecological history/estrogen status
- Association with other voiding and storage symptoms
- Association with other diseases
- Prior surgery
- Pelvic radiation
- Neurological disease
- Prior therapy

Other history

Gynaecological history
- Pelvic organ prolapse
- Previous surgery

Obstetric history
- Labor duration
- Mode of delivery
- Birthweight of children
- Year of delivery
- Intrapartum complication (anal sphincter injury, periurethral injury, wound breakdown)
- De novo postpartum urinary symptoms (urinary retention requiring prolonged catheterization or stress urinary incontinence (SUI)

Psychiatric history
- Depression
- Dementia
- Anxiety

Medical history
- Cardiac history – Prolonged QT interval
- Uncontrolled hypertension
- Functional gastrointestinal pathology
- Myasthenia Gravis
- Uncontrolled narrow angle glaucoma
- Renal impairment
- Liver impairment

Medication/Drug history
- Decreased urethral pressure (neuroleptics, benzodiazepines, α-adrenergic blockers)
- Excess urine production (diuretics)
- Incomplete bladder emptying (β-blockers, anti-Parkinson's agents)
- Drugs with indirect effects such as ACE inhibitors causing cough, narcotics causing constipation, and lithium causing excess fluid intake

Assessment of comorbidities

Neurological diseases
- Stroke
- Parkinson's disease
- Multiple sclerosis
- Spinal cord injury

Urological conditions
- Urolithiasis (painless hematuria)
- Bladder cancer (painless hematuria)
- Recurrent urogenital infections

Endocrine disorders
- Complicated and uncontrolled diabetes
- Diabetes Insipidus

Respiratory dysfunction with chronic cough
- Chronic obstructive pulmonary disease

Pelvic
- Chronic pelvic pain
- Mobility deficits
- Prior pelvic surgeries
- Pelvic cancer
- Pelvic irradiation

Fecal motility disorders
- Constipation
- Fecal incontinence

Physical exam

A physical examination should be performed on the first visit.

Listening to the patient's history in her own words and watching patients walk and climb onto the examining table serve as critical assessments of frailty that is integral for the treatment. The abdomen and pelvis should be palpated, and stirrups and speculum are not used.[22] The internal examination allows for multiple components to be assessed, the most important of which is the patient's ability to identify and voluntarily contract the pelvic floor. If the patient is unable to isolate these muscles, referral to a physical therapist is warranted for pelvic floor training for urge suppression.

Pelvic masses, prior anti-incontinence procedures, high-grade prolapse, and prostatomegaly can also cause obstruction of the outlet with secondary urge and frequency symptoms, which can be misdiagnosed as OAB.[22]

- **Physical examination** - focused examination on the organ systems that may be implicated in urinary incontinence.
- **Abdominal examination** - for scars, masses such as uterine fibroids, hernias, and distension of the bladder.
- **Neurological screen** for upper motor lesions such as Parkinson's disease, and a neurological screen for lower motor lesions such as sacral-nerve root lesions.
- **Rectal examination** can determine the anal sphincter tone. Fecal impaction distends the distal sigmoid and rectum, resulting in inadequate detrusor activity and compromised bladder emptying.
- **Vaginal examination** will reveal a prolapse of pelvic organs because both cystocele and rectocele may impair bladder emptying, and show evidence of urine leakage.

RECOMMENDATIONS

A careful, directed physical exam should include an abdominal exam,
a rectal/genitourinary exam, and an assessment of lower extremities for edema.

Voiding diaries

A bladder diary obtained before the first clinic visit is invaluable for achieving efficient visit and appropriate diagnosis at that first visit. The diary provides symptom documentation such as number of voids per day, the number of incontinent episodes per day, functional bladder capacity and nocturia, and allows for the differentiation of nocturnal polyuria from OAB.

Micturition time charts, frequency/volume charts - 3 day record of intake and voiding behavior is important to monitor treatment response.

Important points noted:	Information achieved from the diaries
• Time • Type • Vol of fluid intake • Urine volume voided • Urgency episodes • Incontinence episodes	• No. of voids in daytime • No. of voids in night • Total in 24 hrs • Volume of urine over 24 hr period • Max voided volume • Average voided volume • Median max voided volume • Nocturnal urine volume

Day 1		Date:			
Time	**Urinated in toilet?**	**If urinated in toilet:** Did you have urgency?	**Leaked?**	**IF LEAKED:** Reason for leakage	**IF LEAKED:** Type of leakage (DK-Don't know)
Begin recording at 12:00 midnight					
		☐ Yes ☐ No			☐ Stress ☐ Urge ☐ DK
		☐ Yes ☐ No			☐ Stress ☐ Urge ☐ DK
		☐ Yes ☐ No			☐ Stress ☐ Urge ☐ DK
		☐ Yes ☐ No			☐ Stress ☐ Urge ☐ DK
		☐ Yes ☐ No			☐ Stress ☐ Urge ☐ DK
		☐ Yes ☐ No			☐ Stress ☐ Urge ☐ DK
After 11:50 pm, stop recording					

A bladder diary helps in determining appropriate behavioral strategies and as an internal control of symptoms and their resolution. The patient should be given a bladder diary to be completed for two consecutive days before the first visit.[22]

RECOMMENDATIONS

Diaries that document intake and voiding behavior may be useful, particularly for patient education and to document baseline symptoms and treatment efficacy.

Symptom questionnaires

The 33-item Overactive Bladder questionnaire (OAB-q; 1-week recall version) has been psychometrically validated in middle-aged. The OAB-q demonstrates reliability, concurrent and discriminant validity, and responsiveness to treatment. The evidence shows that the OAB-q is psychometrically sound for use in medically complex elderly patients with OAB.[23]

RECOMMENDATIONS

Validated symptom questionnaires are useful in the quantification of bladder symptoms and bother changes with OAB treatment.

Clinical evidence

Detrusor overactivity results from an efferent (motor) hyperfunction/dysfunction and also by afferent (sensory) noise. Patients with OBS respond to antimuscarinic treatment irrespective of the presence of detrusor overactivity, urge urinary incontinence, older age, obesity, and chronic constipation. The risk factors for OBS include vaginal birth delivery, with 40% of parous women experiencing.[24]

Investigations

Initial investigations	Secondary investigations
• Urinalysis to exclude infection, hematuria and glycosuria • Urinary tract ultrasound and measurement of postresidual volume • Frequency/volume chart for at least 3 days	• Urine cytology • Imaging of upper urinary tract or spine • Urodynamic testing • Cystoscopy

Urinalysis

A urinalysis to rule out UTI, hematuria and glycosuria should be performed. If evidence of hematuria not associated with infection is found, then the patient should be referred for urologic evaluation.

RECOMMENDATIONS

A urine culture may be appropriate in certain patients given that a urinalysis may be unreliable.

Urine culture

Urine culture help distinguish OAB from UTI.

Urine cytology

- Not routinely recommended
- Performed on three voided specimens obtained on three separate days, has a variable sensitivity for the detection of urothelial carcinoma.
- Urine cytology is effective for screening for tuberculosis, high grade lesions (sensitivity at least 90%, specificity 98%–100%) and carcinoma in situ.

*** Persistent microscopic hematuria warrants urological reference**

Post-void residual

It is currently recommended that post-void residual urine (PVR) should be measured during the assessment of women complaining of overactive bladder symptoms and anticholinergic medication should be used if PVR is low.[25]

- PVR volume indicates poor voiding efficiency
- May worsen symptoms and increase the risk of UTI, upper urinary tract dilatation, and renal insufficiency.
- Elevated PVR: Multifactorial etiology, but is usually caused by BOO or detrusor underactivity.
- PVR should be evaluated in patients with obstructive symptoms, neurological diagnoses, and history of incontinence surgery.
- **PVR should be measured in the assessment of OAB prior to starting antimuscuranics.**
- Ultrasound measurement of PVR is preferable to catheterization.

PVR	Inference
<50 ml	Normal
50-150 ml	Gray zone (should be investigated)
150-250 ml	Demands attention
>250 ml	Warrants special attention if antimuscarinic treatment is intended and consideration should be made as to the existence of other possible pathologies.

Urodynamics

Urodynamic investigation is the gold standard to objectively diagnose dysfunction of the lower urinary tract. Important role in the assessment and diagnosis of lower urinary tract (LUT) function and dysfunction.

Urodynamic tests include a series of clinical tests, like uroflowmetry, pressure-flow studies (Cystometrogram), and assessment of urethral closure (including urethral pressure profilometry and measurement of the leak-point pressure).

- Not an initial workup in OAB
- Used selectively in refractory cases or neurological domain

According to European Association Urology guidelines, the urodynamics are not necessary to help decide the best treatment for uncomplicated urinary incontinence. However, these urodynamic studies may help if there is any uncertainty over the choice of invasive treatments. The guidelines stress the importance of conducting urodynamic tests to the highest possible quality standards for the results to be useful in the decision-making process.[26]

Cystoscopy and other imaging

- Not recommended routinely
- Cystoscopy exclude other causes (bladder tumour, carcinoma insitu, ulcers, bladder stones, foreign bodies, cystitis) recommended in recurrent UTI, persistent pyuria, hematuria, bladder pain, a history of stress incontinence or pelvic surgery, suspected fistula, urethral diverticulum, or urinary tract malformation.

In patients with possible obstructive pathology.

- CT, MRI – with associated neurological symptoms.

RECOMMENDATIONS

Urodynamics and cystoscopy should not be used in the initial workup of the uncomplicated patient.

Differential diagnosis

The importance of distinguishing OAB from other conditions presenting with similar symptoms is key in preventing misdiagnosis, treatment delays, and antibiotic overuse.[27]

- Nocturnal polyuria

Nocturnal void are frequently normal or large volume as opposed to small volume voids in OAB.

- Polydipsia-related frequency

Frequency as a result of polydipsia

- Interstitial cystitis/bladder pain syndrome

Dyspareunia or pain on bladder filling are the differentiating symptoms from OAB

- Stress urinary incontinence

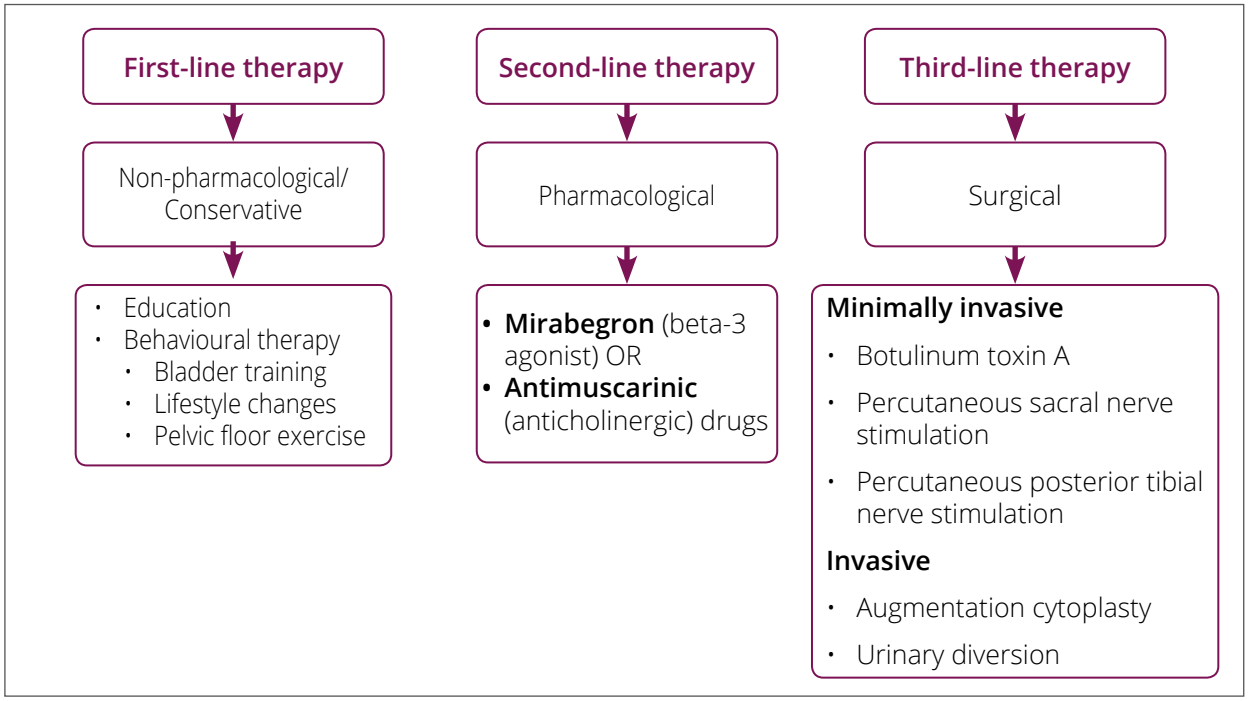
Differentiating OAB from stress incontinence		
Symptoms	**Overactive bladder**	**Stress incontinence**
Urgency (strong, sudden desire to avoid)	Yes	No
Frequency with urgency	Yes	Rarely
Leaking during physical activity e.g., coughing, sneezing, lifting etc.	No	Yes
Amount of urinary leakage with each episode of incontinence	Large, if present	Usually small
Ability to reach the toilet in time following an urge to void	No or just barely	Yes
Nocturnal incontinence (presence of wet pads or undergarments in bed)	Yes	Rarely
Nocturia (waking to pass urine at night)	Usually	Seldom

Clinical evidence

OAB is common urologic condition that should be considered when patients present with UTI symptoms. The women with impaired bladder emptying present with a wide range of lower urinary tract symptoms (LUTS). In such patients post-void residual (PVR) measurement is crucial for diagnosis. OAB and voiding dysfunction can coexist and accurate diagnosis of underlying pathophysiology may also be required.[28]

In postmenopausal women, urinary incontinence, the presence of a cystocele, and postvoid residual volume were strongly associated with recurrent UTI. The gold standard for confirming a UTI remains a positive urine culture.[26]

Management[26]



First-line therapy

Education[27]

Clinicians should provide education to patients regarding normal lower urinary tract function,

what is known about OAB, the benefits versus risks/burdens of the available treatment alternatives and the fact that acceptable symptom control may require trials of multiple therapeutic options before it is achieved.

So the treatment demands patience and motivation for long-term improvements.

RECOMMENDATIONS

Clinicians should provide education to patients regarding normal lower urinary tract function, what is known about OAB, the benefits vs. risks/burdens of the available treatment alternatives and the fact that acceptable symptom control may require trials of multiple therapeutic options before it is achieved.

Behavioural therapy

- Dietary changes and fluid management
- Timed voiding
- Bladder training
- Modification of voiding interval
- Urge control (bladder Inhibition)
- Pelvic floor muscle therapy (PFMT) - With the help of physiotherapist if available

Dietary and fluid intake

- Weight loss in obese patient
- Cessation of smoking
- Avoid bladder irritant (caffeine, alcohol, spicy food, and acidic food)
- Avoid diuretics
- Avoid too much or too little fluid intake
- Treat constipation
- In patient with lower extremity edema elevation of leg before bed time help to prevent nocturia.

Timed (scheduled) voiding

- Voiding by routine schedule with constant interval between void (every 2–3 hours).
- This helps to empty the bladder before incontinence occurs and decrease urgency and frequency.
- Voiding interval may be changed throughout the day to match patients' incontinence pattern.

Bladder training

- It is an intensive behavioral treatment that is recommended for highly motivated adult patients without cognitive or physical impairments.

The goal of bladder training

Restore normal bladder function through a process of education along with a mandatory or self-adjustable voiding regimen that gradually increases the time interval between voids

Two processes

1. **Modification of voiding interval**

- Voiding intervals may be as short as 30 minutes and training may bring a gradual increase of voiding intervals by 15–60 mins every 1–2 weeks until the patient can be in control for periods of 3 to 4 hours, ultimately increasing bladder capacity.

2. **Urge control (bladder inhibition) – Knack Manouever**

- Keeping the body calm until urge subsides.
- Taking slow deep breath.
- Concentration on elimination the urge by mental calculation or mental imaging.
- Contraction of pelvic floor muscle.
- After the urge subsides, don't urinate until the next scheduled void.

Bladder training required a motivated patient with sufficient cognitive function

Possible mechanisms for bladder training for improving LUTS are:

1. Improving central control over bladder sensations and urethral closure.
2. Changing an individual's behavior to increase the LUT system's 'reserve capacity' as knowledge of circumstances that cause bladder leakage is gained.[28]

Clinical evidence of bladder training

Bladder training is a multi component intervention that involves patient education regarding LUT function, setting incremental voiding schedules, and teaching urge control techniques to postpone voiding and adhere to a schedule. Several clinical studies and in randomized control trials using intention to treat models have established the effectiveness of behavioral training with urge suppression as a stand alone strategy for urge urinary incontinence, in which mean reductions of urinary incontinence ranged from 60% to 80%.[29] Although not all patient experience complete symptom relief, most patients experience significant reductions in symptoms and improvements in QoL. The literature provides clear support for the effectiveness of both bladder and behavioral training.[30,31] A bladder training study showed that reducing caffeine intake also resulted in reductions in voiding frequency.[32]

Pelvic floor muscle training

- Kegel exercises
- Vaginal weight training (Vaginal Cones)
- Pelvic floor exercise with biofeedback
- Pelvic-floor electrical stimulation

It helps in reducing detrusor contractions through inhibitory reflexation of the pelvic floor. Patient is taught to tighten their pelvic floor muscles when they experience an involuntary contraction. It Reduces episodes of urgency and urge incontinence. It consists of intermittent voluntary maximal contraction of pelvic floor muscles. Each contraction is held 6-8 seconds and followed by brief period of relaxation. A common regimen is set of 10 contractions 3 times per day. Continence is found to improve in 6-12 weeks after pelvic floor muscle training.

Clinical evidence of behavior therapy

According to researchers' relatively minor weight loss of 8% in obese woman reduced overall incontinence episodes per week and urgency urinary incontinence episodes by 47% and 42% vs.

28 and 26% in controls.[33] The literature review of comparative effectiveness randomized trials indicates that behavioral treatments are equivalent[34-36] or superior to[37,38] medical treatment in terms of reducing incontinence episodes, improving frequency and nocturia[39] and improving QoL.

Fluid management with a 25% reduction in fluid intake reduced frequency and urgency.[40]

RECOMMENDATIONS

Clinicians should offer behavioral therapies (e.g. bladder training, bladder control strategies, pelvic floor muscle training, and fluid management) as first-line therapy to all patients with OAB

Second-Line therapy - Pharmacological treatment of OAB

Pharmacological management of uncomplicated OAB involves the use of mirabegron (the first clinically available β-3 agonist) or antimuscarinic (anticholinergic) drugs as the mainstays of drug treatment for urge urinary incontinence (UUI).[41]

Mirabegron is a selective β3-adrenoceptor agonists that have an activity different than that of antimuscarinics. It causes increased cyclic adenosine monophosphate concentrations in the bladder tissue and shows a bladder relaxant effect. It also results in relaxation of bladder smooth muscle and enhancing bladder relaxation during the storage phase of micturition.[42]

Preclinical and clinical studies showed β3 adrenoceptor agonists have no significant negative effect on the voiding contraction, therefore limiting the risk of urinary retention. β3 adrenoceptor agonists have a pronounced effect on spontaneous contractile activity in the detrusor muscle in vitro therefore reducing the bladder tone and afferent input, which is related to the storage symptoms of the OAB syndrome.[43]

RECOMMENDATIONS

Mirabegron (the first clinically available β3 agonist) OR antimuscarinic drugs are the mainstays of drug treatment for UUI.

Anticholinergic drugs stabilize the detrusor muscle by binding and blocking muscarinic receptors, resulting in the improvement of bladder functional capacity, reduction of detrusor overactivity, and improvement of symptoms**.** Many concerns have been raised regarding the use of antimuscarinic medications in the frail elderly. Apart from the 'classic' side-effects of dry mouth and constipation, elderly patients can also experience impaired attention, delayed memory, visual disturbances, dizziness, and somnolence. Many of the frail elderly are already taking various medications for

other conditions, and interaction with certain drugs (eg, antidepressants, antihistaminic agents, and medication for Parkinson's disease) leads to an increased risk of antimuscarinic side effects.[44]

A novel agent such as β3 -adrenoceptor agonists is an alternative option for women not responding to or experiencing serious side effects to antimuscarinics.

Summary for pharmacotherapy for OAB[45]

β3 receptor agonist medications for OAB

Medication	Dosage and administration	Site of action	Metabolism and dose considerations	Main side effects
Mirabegron	25–50 mg daily Take with or without food	β3 adrenergic receptor agonist	• Hepatic • Maximal dose 25 mg daily if severe renal impairment (CrCl <30 mL/min) or moderate hepatic impairment • Not recommended in end stage renal failure or severe hepatic impairment • Monitor drugs metabolized by CYP2D6b (inhibited by mirabegron)	All low incidence • Hypertension • Tachycardia • Urinary tract infection • Constipation or diarrhea • Nasopharyngitis

Antimuscarinic medications for overactive bladder

Medication	Dosage and administration	M receptor affinity					Metabolism and dose considerations	Main side effects
		M1	M2	M3	M4	M5		
Oxybutynin IR	2.5–5 mg bid–tid	*	*	*	*		Hepatic Caution in renal or hepatic disease	Dry mouth +++ Constipation++ Cognitive ++
Oxybutynin ER	5–30 mg daily	*	*	*	*		Hepatic Not studied in renal or hepatic impairment	Dry mouth +++ Constipation++ Cognitive ++
Tolterodine ER	2–4 mg daily	*	*	*		*	Hepatic Maximal dose 2 mg/ daily if severe renal impairment (CrCl <30 mL/min) or significant hepatic impairment or on potent CYP3A4 inhibitors	Dry mouth ++ Constipation + Cognitive: no effect Prolonged QT interval (dose ≥8 mg/d)

Medication	Dosage and administration	M receptor affinity					Metabolism and dose considerations	Main side effects
		M1	M2	M3	M4	M5		
Solifenacin	5–10 mg daily			*			Hepatic Maximal dose 5 mg if severe renal impairment (CrCl <30 mL/min) or mod hepatic impairment or on potent CYP3A4 inhibitors	Dry mouth + Constipation + Cognitive: no effect
Darifenacin	7.5–15 mg daily			*			Hepatic Maximal dose 7.5 mg if moderate hepatic impairment or on potent CYP3A4 inhibitors	Dry mouth + Constipation+/++ Cognitive: no effect

Nonantimuscarinic medications for OAB

Medication	Dosage and administration	Site of Action	Metabolism and dose considerations	Main side effects
Botulinum toxin A	100–200 U idiopathic OAB 200–300 U neurogenic OAB	Presynaptic motor neuron	May repeat >12 weeks after previous treatment when symptoms return Patient/caregiver able to perform CIC or patient willing to have IDC in case of urinary retention	• Urinary retention (elevated PVR ± need for CIC) • Hematuria • Urinary tract infection
Tricyclic antidepressant	Starting doses • Imipramine 10 mg/bid • Amitriptyline 10–20 mg/day	Central action (multiple receptors in CNS) and direct action on detrusor	Hepatic Caution with coadministration of anticholinergic agents or sedatives, in elderly patients, preexisting cognitive decline or cardiac arrhythmia	• Anticholinergic side effects • Tremor • Arrhythmia • Nausea

CIC: clean intermittent catheterization; CNS: central nervous system; IDC: indwelling catheters; OAB: overactive bladder; PVR: postvoid residual.

Anticholinergic cognitive burden (ACB)

ACB scale is a practical tool used to identify the severity of anticholinergic effects on cognition. It provides clinicians with a score that captures the accumulative ACB resulting from the total medications taken by older adults.

Scoring	Description
0	Drugs with no anticholinergic effects
1	Drugs with possible anticholinergic effects (affinity for muscarinic receptors but no clinically relevant negative cognitive effects)
2 and 3	Drugs with established and clinically relevant cognitive anticholinergic effects Based on blood-brain barrier permeability and association with the development of delirium

The total added score of different drugs taken by patient determines the accumulative anticholinergic cognitive burden.

Interpreting the results

- Each definite anticholinergic may increase the risk of cognitive impairment by 46% over 6 years
- For each 1 point increase in ACB total score, a decline in MMSE (Mini-Mental state examination) of 0.33 points over 2 years
- Each 1 point increase in the ACB total score has been correlated with a 26% increase in risk of death

β3-adrenoceptors agonists

Mirabegron is the first β3-adrenoceptor agonist that is approved for use in OAB. It is a selective β3-adrenoceptor agonists that have an activity different than antimuscarinics.

The detrusor muscle and the urothelium show the presence of all three β3-adrenoceptor agonists (β 1, β 2 and β 3) and the β-adrenoceptor messenger RNA (mRNA) has prominent presence in human bladder tissue, with 97 % of total β-adrenoceptor mRNA being represented by the β3 adrenoceptor subtype and only 1.5 and 1.4 % by the β1 adrenoceptor and β2 adrenoceptor subtypes, respectively.[44]

β3 adrenoceptor activation and the subsequent activation of adenylyl cyclase that catalyzes the conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) causes bladder relaxation. Additionally, the cAMP-dependent pathway is involved in the β3 adrenoceptor ago β3-adrenoceptor agonist-induced detrusor muscle relaxation.[44] Mirabegron can also inhibit mechanosensitive bladder afferent activity which may be related to suppression of bladder micro-contractions.[44]

RECOMMENDATIONS STRONG LEVEL A

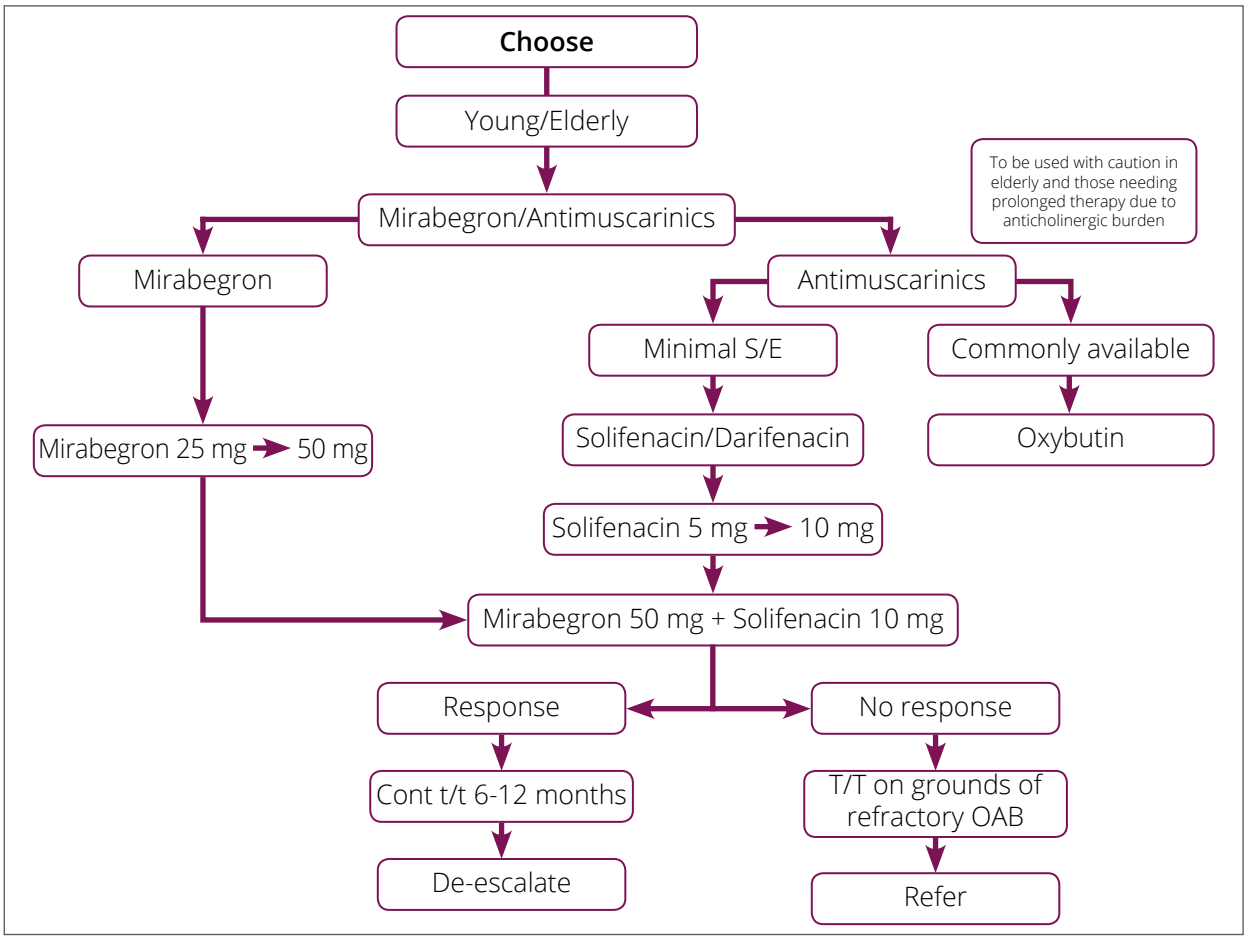
Mirabegron improves the OAB symptoms in both naïve patients and those who discontinued primary antimuscarinic therapy.

It has better efficacy when prescribed as first-line therapy

Pharmacological interventions in women

Mirabegron as first-line therapy

In a study, researchers evaluated the efficacy of mirabegron in treatment-naive patients in comparison with those who had discontinued antimuscarinic therapy because of insufficient efficacy.[45] The women participating in the study were divided into two groups: women without any previous pharmacological treatment for OAB (group 1) and women with a previous history of failed antimuscarinics therapy (group 2). Researchers concluded that mirabegron is efficacious in improving OAB symptoms in both naïve patients and those who discontinued primary antimuscarinic therapy; however, its efficacy is superior when prescribed as first-line therapy.



OAB in elderly

The OAB symptom complex is increasingly prevalent in association with increasing age. Older people experience a more severe degree of incontinence, including OAB, as compared to younger patients. Older people may experience severe urge, rather than urgency, as defined by the International Continence Society.

In older individuals with OAB, bladder sensation appears to be heightened, bladder capacities much lower, and urethral resistance rises in association with the onset of the condition.

Treatment of OAB

- In choosing antimuscarinic therapy, cognitive functions of patients should be taken in to consideration for elderly patients.[46] Conservative and lifestyle measures sometimes may effective in older people.
- Elderly people may require higher doses of medication.[46]
- Due to potential CNS adverse effects of anticholinergic agents, increased cognitive burden complete evaluation of benefits and risks to be done in elderly frail patients.
- Mirabegron 25 mg and 50 mg showed similar efficacy in UUI treatment in the population >65 years and >75 years when compared with the overall population and should be considered to treat UUI in elderly.

Mirabegron has also been studied in elderly patients with OAB. Wagg et al. evaluated the efficacy and tolerability of mirabegron in subgroups of patients aged >65 years and >75 years. Over a 1-year period, the incidence of the most common adverse events between both doses of mirabegron was similar to placebo, and there appeared to be no loss of efficacy with age. In addition, Matsuo et al. evaluated the use of mirabegron in an elderly population of male patients with lower urinary tract symptoms and persistent OAB symptoms regardless of the use of α1-adrenergic receptor blocker. Mirabegron was shown to be effective in reducing OAB symptoms and had no negative effects on voiding function. The therapeutic effect was not correlated with patient's age. Thus, mirabegron might be a valuable drug in elderly patients with OAB and a high anticholinergic burden.[46]

RECOMMENDATIONS

When starting anticholinergics in elderly patients, the number of medications that have anticholinergic effects and their cumulative effects on mental function should be assessed objectively and monitored. Mirabegron 25 mg and 50 mg showed similar efficacy in UUI treatment in the population >65 years and >75 years when compared with the overall population and should be considered to treat UUI in elderly patients.

Refractory OAB

Approximately 25%–40% of patients fail to achieve satisfactory improvement in incontinence with anticholinergics.[47]

If the patients failing on anticholinergic therapy then mirabegron can be considered as alternative therapy. Mirabegron can be tried at dose of 25 mg initially up to 8 weeks and patient response evaluated. After 8 weeks of treatment, the mirabegron dose could be increased to 50 mg if the patient's symptom improvement was not sufficient. If after dose escalation of mirabegron at 50 mg dose not yield the desired results solifenacin can be added to therapy.[48]

The recommended starting doses for combination treatment are Mirabegron 25 mg once daily and solifenacin succinate 5 mg once daily. Based on individual patient efficacy and tolerability, the mirabegron dose may be increased to 50 mg once daily after 4 to 8 weeks.[49]

Third-line therapies are recommended in patients who had failed to respond to conservative treatments. These therapies include:

- Intravesical botulinum toxin type A (BoNT-A),
- Posterior tibial nerve stimulation (PTNS),
- Sacral neuromodulation (SNM),
- Augmentation cystoplasty, and
- Urinary diversion

Treatment choice is based on several multiple factors such as patient preference, surgical expertise, available resources, and financial considerations.

Treatment of refractory OAB includes SNM, PTNS, Intravesical botulinum toxin injection, augmentation cystoplasty, and urinary diversion. Sacral neuromodulation is highly effective and safe in the management of urgency incontinence as well as an urgency-frequency syndrome. PTNS, a peripheral neuromodulation technique is effective in the management of refractory OAB.

Botulinum toxin A

Intradetrusor injection of botulinum toxin A may serve as a minimally invasive substitute in women with refractory idiopathic OAB.[50]

Elderly and/or multiparous women are at increased risk of urinary retention after intravesical 100-U Botox injections.[51]

Botulinum toxin A (BoNT-A) is a neurotoxic protein that inhibits the release of vesicular acetylcholine from somatic and autonomic presynaptic nerve terminals. BoNT-A is widely used in the treatment of neurogenic bladder dysfunction and idiopathic OAB.[52] In a randomized control trial, 80% of OAB patient treated with 100 -300 U of Botulinum toxin (injected into the detrusor muscle) showed a significant reduction in the number of voids, urgency, and incontinence episodes per day and also showed greater improvement in maximum cystometric capacity and quality of life. Transient urinary retention is the most commonly reported complication associated in OAB patient treated with intravesical BoNT-A.[53] Similarly, Makovey et al compared the efficacy of BoNT-A with the efficacy of antimuscarinic therapy in 85 patient with refractory OAB and reported that 86% of patient are more likely to respond to BoNT-A therapy as compared to 60% in antimuscarinic therapy.[54]

Peripheral tibial nerve stimulation

Percutaneous tibial nerve stimulation (PTNS) involves insertion of a 0.22 mm needle at about ≈5 cm above the medial tibial malleolus, approximated as three finger breadths. The needle is connected to an electric generator producing external pulses of 0–10 mA. This voltage is increased until the response is achieved in the form of flexor muscle contraction of the first toe, fanning of all toes, or tingling sensation in the sole. At this point, the voltage remains at one point below the stimulus that generated the muscular contraction.[55] The PTNS improves diurnal frequency, urgency, and urge incontinence.

Clinical evidence of PTNS

Researchers have reported a significant improvement in refractory OAB using PTNS as compared to antimuscarinic. In a randomized, multicentre, double-blind trial, researchers reported a statically significant improvement in frequency, night-time voids, and UUI (episodes in PTNS group (n=220) as compared to sham therapy. Similarly, in orbit trials, 79.5% of patients treated with PTNS group showed a statically significant improvement in patients with OAB associated symptoms (incontinence episodes, frequency, and urgency) as compared to 54.8% in the tolterodine group ($p = 0.01$). Recent guidelines by the European Association of Urology (EAU) have recommended PTNS as a treatment option for the improvement of urinary incontinence in women who have not benefited from antimuscarinic medication.[52]

Researchers have determined the efficacy of PTNS as a treatment for the OAB resistant to medical treatment. The study participants (n=60) underwent 12 sessions of PTNS using a personal computer-based system, and these patients were reassessed after the sixth session, at the end of the course, and at 3 and 6 months after the last session. The researchers have reported that there was a statistically significant improvement in all the variables assessed. The PTNS is reported to be safe and provides statistically significant improvements in the patient's assessment of OAB symptoms.[55]

The PTNS is an established treatment for OAB, especially in women with other concomitant pelvic disorders, such as sexual impairment.[56]

Sacral neuromodulation

When patients are carefully chosen, sacral neuromodulation provides the greatest benefit to patients with wet OAB. However, in mixed urinary incontinence or solitary stress urinary incontinence, sacral neuromodulation has not shown substantial efficacy. Sacral neuromodulation has greater benefit in younger individuals or those with less severe cognitive deficit. Sacral neuromodulation improves most clinical voiding parameters in patients for both OAB and urinary retention.[57]

Clinical evidence of Sacral neuromodulation

Siegel et al conducted a study on patients with refractory OAB (n=147) and compared the results of OAB treated with SNM (n=70) and standard medical therapy (SMT) (n=77). About 61% of patients treated with SNM group showed significantly greater success rate at 6 months as compared to 42% in SMT group ($p = 0.02$). Although SNM therapy is highly effective, a patient treated with SNM showed 30.5% of adverse effects (undesirable change in stimulation, implant site pain, and lead migration) after implantation as compared to 27.3% in SMT group.[58]

In a prospective study of 55 patients with refractory urge incontinence who responded to sacral neuromodulation found that the cure rate was associated with age. The patients who were younger than 55 years had a statistically significant higher cure rate of 65% as compared to older (>55 years) patients who had a cure rate of 37%.[59] Sherman et al assessed 34 patients experiencing refractory UUI after surgery for stress incontinence who underwent neuromodulator placement. Researchers found that 59.1% of patients who had improvement were aged >55 years and 100% of patients older than <55 years did not show any improvement.[60]

Additionally, researchers have shown that sacral neuromodulation has greater benefit in younger individuals or those with less severe cognitive deficits.[61] In an observational, retrospective, double cohort review of 339 female women who had experienced medically recalcitrant OAB or urinary retention symptoms, researchers have shown a significant improvement in the symptoms. While most patients improvement (up to 40%) in most clinical voiding parameters in the <3 voltage patients for both OAB and urinary retention.[57]

Augmentation cystoplasty and urinary diversion

According to "American Urological Association" guidelines, augmentation cystoplasty or urinary diversion is rarely used as a treatment option in severe, refractory, and complicated OAB patients.[52]

Augmentation cystoplasty

- The bladder capacity is increased by bivalving the bladder wall and replacing it with a segment of bowel.
- Incorporation of bowel segment also has the potential of diminishing detrusor contractility.
- In clinical practice, ileum is often the most commonly used segment of bowel in adult patients.

Urinary diversion

- Usually this will utilize an ileal conduit to create an abdominal stoma for urinary diversion.
- An alternative is to form a continent diversion using the appendix or ileum which may then be drained using self-catheterization.

Studies comparing the treatments of refractory OAB is provided in Table no 1[52]

An overview of the possible treatments for refractory OAB[46]

	SNM	PTNS	BoNT-A
FDA/EC approval	Yes	Yes	Yes
Long-term results	Yes	No	Limited
Advantages	Minimally invasive Works for both urinary and bowel disorders	Non-invasive, simple	Minimally invasive Direct effect
Disadvantages	Permanent implant Battery replacement every 5-8 yr	Repeat after 8-12 wks Inferior efficacy	Repeat after 6-12 month Need for CISC
Reversibility	Removal of implant	Instantly	After 6 month
Adverse events	Wound infection Device-related pain Device malfunction	None	Urinary retention Urinary tract infection Hematuria

BoNT-A: botulinum toxin type A; CISC: clean intermittent self-catheterization; EC: European Commission; FDA: Food and Drug Administration; OAB: overactive bladder syndrome; PTNS: posterior tibial nerve stimulation; SNM: sacral neuromodulation

Conclusion

To summarize, our knowledge of the OAB syndrome has increased immensely over recent years. New OAB discoveries might help us make an earlier diagnosis, prevent progression, predict treatment response, and obtain better outcomes. As researchers begin to systematically explore both the genome and the metabolome of the urinary tract, with a special attention to transitional studies and clinical research, we will probably expect great improvement of our practice and in OAB patients' relief in the future.

References

1. University of Oxford, Graduate School in EBM and Research Methods, Centre for Evidence-Based Medicine [Internet]; Oxford Centre for Evidence-based Medicine – Levels of Evidence and Grades of Recommendation, Published 2009; Cited December 2016. Available from: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed March 23, 2017. **2.** Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010;29:4–20. **3.** Leron E, Weintraub AY, Mastrolia SA, Schwarzman P. Overactive bladder syndrome: Evaluation and management. Curr Urol. 2017;11(3):117–25. **4.** Lapitan MC, Chye PL. The epidemiology of overactive bladder among females in Asia: a questionnaire survey. Int Urogynecol J Pelvic Floor Dysfunct. 2001;12:226-31 **5.** Ubee SS, Manikandan R, Singh G. Medical management of overactive bladder. 2010; 26(2):270–78. **6.** Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 2003;20:327–36. **7.** Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder and other lower urinary tract symptoms in five countries: Results of the EPIC study. Eur Urol. 2006;50(6):

1306–1315. **8.** Irwin DE, Abrams P, Milsom I, Kopp Z, Reilly K, EPIC Study Group. Understanding the elements of overactive bladder: Questions raised by the EPIC study. BJU Int. 2008;101(11):1381–387. **9.** Sexton CC, Coyne KS, Vats V, et al. Impact of overactive bladder on work productivity in the United States: results from EpiLUTS. Am J Manag Care. 2009 ;15(4 Suppl):S98-S107. **10.** Milsom I, Abrams P, Cardozo L, et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population based prevalence study. BJU Int. 2001;87(9):760–66. **11.** Haylen BT, de Ridder D, Freeman Rm, et al. An International urogynecological Association (IuGA)/ International continence Society (IcA) joint report on the terminology for female pelvic floor dysfunction. Int urogynecol J. 2010;21:5–26. **12.** Hashim h, Abrams P. Overactive bladder: An update. curr Opin urol 2007;17:231–36. **13.** Ballert K, Biggs G, Nitti V. Antimuscarinic agents. AuA update series 2008;27:137–47. **14.** de Groat WC. A neurologic basis for the overactive bladder. Urology 1997;50(6A suppl):36–52. **15.** Brading AF. Spontaneous activity of lower urinary tract smooth muscles: Correlation between ion channels and tissue function. J Physiol. 2006;570:13–22. **16.** Drake MJ, Mills WI, Gillespie JI. Model of peripheral autonomous modules and a myovesical plexus in normal and overactive bladder function. Lancet. 2001;358:401–03. **17.** Andersson KE. Detrusor myocyte activity and afferent signaling. Neurourol Urodyn. 2010;29:97–106. **18.** Wein AJ, Rackley RR. Overactive bladder: A better understanding of pathophysiology, diagnosis and management. J Urol. 2006;175: S5–10. **19.** Chapple C, Gormley EA. Developments in pharmacological therapy for the overactive bladder. BJU Int. 2006;98 (1 Suppl):78–87. **20.** Abrams P, Andersson KE. Muscarinic receptor antagonists for overactive bladder. BJU Int 2007;100:987–1006. **21.** Nitti V. Clinical testing for overactive bladder. Can Urol Assoc J. 2011; 5(5 Suppl 2): S137–S138. **22.** Lightner DJ, Agarwal D, Gormley EA. The overactive bladder and the AUA guidelines: A proposed clinical pathway for evaluation and effective management in a contemporary urology practice. Urology Practice. 2016; 3:399–405. **23**. Barsdorf AI, Carlsson M, Bushmakin AG, et al. Validation of overactive bladder questionnaire (1-week recall version) in medically complex elderly patients with overactive bladder. Int Urogynecol J. 2017;28(12):1857–863. **24.** Arnold J, McLeod N, Thania-Gasalam R, Rashid P. Overactive bladder syndrome: Management and treatment options. Australian Family Physician. 2012; 41(11): 878–83. **25.** Milleman M, Langenstroer P, Guralnick ML. Post-void residual urine volume in women with overactive bladder symptoms. J Urol. 2004;172(5 Pt 1):1911–14. **26.** Gray MG, Dieter AA, Geller EJ.Evaluation and management of overactive bladder: Strategies for optimizing care. Res Rep Urol. 2016; 8: 113–122. **27.** Gormley EA, Lightner DJ, Burgio KL et al. Diagnosis and treatment of non-neurogenic overactive bladder (OAB) in adults: AUA/SUFU Guideline. AUA/SUFU Guideline: Published 2012; Amended 2014. **28.** https://www.slideshare.net/MohamedElgendy18/oveactive-bladder. **29.** Newman DK, Borello-France D, Sung VW. Structured behavioral treatment research protocol for women with mixed urinary incontinence and overactive bladder symptoms. Neurourol Urodyn. 2018;37(1):14–26. **30.** Jarvis GJ. A controlled trial of bladder drill and drug therapy in the management of detrusor instability. Brit J Urol. 1981; 53: 565. **31.** Burgio KL, Goode PS, Johnson TM 2nd et al. Behavioral versus drug treatment for overactive bladder in men: The male overactive bladder treatment in veterans (MOTIVE) trial. J Am Geriatr Soc. 2011; 59: 2209. **32.** Bryant CM, Dowell CJ, Fairbrother G. Caffeine reduction education to improve urinary symptoms. Br J Nurs. 2002; 11: 560. **33.** Fantl JA, Wyman JF, McClish DK et al. Efficacy of bladder training in older women with urinary incontinence. JAMA. 1991; 265: 609. **34.** Kaya S, Akbayrak T, Beksac S. Comparison of different treatment protocols in the treatment of idiopathic detrusor overactivity: A randomized controlled trial. Clin Rehabil. 2011; 25: 327. **35.** Arruda RM, Castro RA, Sousa GC et al. Prospective randomized comparison of oxybutynin, functional electrostimulation, and pelvic floor training for treatment of detrusor overactivity in women. Int Urogynecol J Pelvic Floor Dysfunct. 2008; 19: 1055. **36.** Colombo M, Zanetta G, Scalambrino S et al. Oxybutynin and bladder training in the management of female urge urinary incontinence: A randomized study. Int Urogynecol J. 1995; 6: 63. **37.** Burgio KL, Locher JL, Goode PS et al. Behavioral vs drug treatment for urge urinary incontinence in older women: A randomized controlled trial. JAMA 1998; 280: 1995. **38.** Subak LL, Wing R, West DS et al. Weight loss to treat urinary incontinence in overweight and obese women. NEJM. 2009; 360: 481. **39.** Johnson TM, Burgio KL, Goode PS et al. Effects of behavioral and drug therapy on nocturia in older incontinent women. J Am Geriatr Soc. 2005; 53: 846. **40.** Hashim H and Abrams P. How should patients with an overactive bladder manipulate their fluid intake? Brit J Urol. 2008; 102: 62. **41.** Nambiar AK, Bosch R, Cruz F, et al. EAU Guidelines on assessment and nonsurgical management of urinary incontinence. Eur Urol. 2018;73(4):596–609. **42.** Sharaf A, Hashim H. Profile of mirabegron in the treatment of overactive bladder: place in therapy. Drug Des Devel Ther. 2017;11:463-67. **43.** Warren K, Burden H, Abrams P. Mirabegron in overactive bladder patients: Efficacy review and update on drug safety. Ther Adv Drug Saf. 2016; 7(5): 204–16. **44.** Marcelissen T, Rashid T, Antunes Lopes T et al. Oral pharmacologic management of overactive bladder syndrome: Where do we stand? Eur Urol Focus. 2018 Apr 4. pii: S2405-4569(18)30089-0 **45.** Bridgeman MB, Friia NJ, Taft C et al. Mirabegron: β3-adrenergic receptor agonist for the treatment of overactive bladder. Ann Pharmacother. 2013;47(7-8):1029–38. **46.** Wagg. A, Tincello DG. Treating overactive bladder in the elderly. Can Urol Assoc J. 2011 Oct; 5(5 Suppl 2): S149–S151. **47.** Julie Wong et al. Management of refractory overactive bladder. The Obstetrician and Gynaecologist 2016;18:173–81. **48.** Mirabegron PI. Available at: https://www.us.astellas.com/docs/Myrbetriq_WPI.pdf. Accessed on 20 Feb, 2019. **49.** Abrams P, Kelleher C, Staskin D et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: Efficacy and safety results from a randomised, double-blind, dose-ranging, phase 2 study (Symphony). Eur Urol. 2015;67(3):577–88. **50.** Zargham M, Abedi S, Alizadeh F, et al. Is there any relationship between bladder trabeculation and efficacy and safety of intravesical botulinum toxin a injection in refractory idiopathic overactive bladder women? Adv Biomed Res. 2017;6:113. **51.** Miotla P, Cartwright R, Skorupska K, et al. Urinary retention in female OAB after intravesical Botox injection: Who is really at risk? Int Urogynecol J. 2017;28(6):845–50. **52.** Marcelissen T, Cornu JN, Antunes-Lopes T, et al. Management of idiopathic overactive bladder syndrome: What is the optimal strategy after the failure of conservative treatment? Eur Urol Focus. 2018; 4(5):760–67. **53.** Geoffrion R. Treatments for overactive bladder: Focus on pharmacotherapy. J Obstet Gynaecol Can. 2018; 40(1):e22–e32. **54.** Makovey I, Davis T, Guralnick ML et al. Botulinum toxin outcomes for idiopathic overactive bladder stratified by indication: Lack of anticholinergic efficacy versus intolerability. Neurourol Urodyn. 2011; 30: 1538–40. **55.** Sherif H, Abdelwahab O. Posterior tibial nerve stimulation as treatment for the overactive bladder. Arab J Urol. 2013; 11(2): 131–35. **56.** Musco S, Serati M, Lombardi G, et al. Percutaneous tibial nerve stimulation improves female sexual function in women with overactive bladder syndrome. J Sex Med. 2016;13(2):238–42. **57.** Marinkovic SP, Ford JC. Improving clinical outcomes for women with overactive bladder or urinary retention symptoms: A comparison of motor response voltages (1-9 V) during Stage 1 sacral neuromodulation. BJU Int. 2018;122(3):472–79. **58.** Siegel S, Noblett K, Mangel J, et al. Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. Neurourol Urodyn 2015; 34: 224–30. **59.** Amundsen CL, Romero AA, Jamison MG, Webster GD. Sacral neuromodulation for intractable urge incontinence: Are there factors associated with cure? Urology. 2005;66(4):746–50. **60.** Sherman ND, Jamison MG, Webster GD, Amundsen CL. Sacral neuromodulation for the treatment of refractory urinary urge incontinence after stress incontinence surgery. Am J Obstet Gynecol. 2005;193(6):2083–087. **61.** Sukhu T, Kennelly MJ, Kurpad R. Sacral neuromodulation in overactive bladder: A review and current perspectives. Res Rep Urol. 2016; 8: 193–99.

For OAB patients with

- Urgency
- Overflow
- Leakage
- Nocturia

Rx OAB-F™

Mirabegron Extended Release 25mg/50mg Tablets

First Line Management for Overactive Bladder

- Novel mechanism of action & proven efficacy across multiple RCTs
- Superior treatment adherence for OAB
- Lower incidences of adverse events as compared to antimuscarinics

Dosage

Recommended by FDA

25/50mg
Once a Day with or without food
Depending on severity of symptoms

Symptoms are controlled within 7 days[1]

ABRIDGED PRESCRIBING INFORMATION FOR OAB-F

Composition: Mirabegron (Extended Release) 25 mg and 50 mg tablets for oral use.

Indications and uses: OAB-F is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. **Dosage and Administration:** Recommended starting dose is 25 mg once daily, with or without food. 25 mg is effective within 8 weeks. Based on individual efficacy and tolerability, may increase dose to 50 mg once daily. Swallow whole with water, do not chew, divide or crush. Patients with Severe Renal Impairment or Patients with Moderate Hepatic Impairment: Maximum dose is 25 mg once daily. **Contraindication:** Hypersensitivity reactions.**Warnings and Precautions**: *Increases blood pressure*: OAB-F can increase blood pressure. Regular blood pressure evaluations recommended, especially for hypertensive patients. Not recommended for use in severe hypertension patients. *Urinary retention in Patients with Bladder Outlet Obstruction and in Patients Taking Antimuscarinic Drugs for Overactive Bladder:* Administer with caution. *Angioedema*: Angioedema of the face, lips, tongue and/or larynx has been reported with OAB-F. *Patients Taking Drugs Metabolized by CYP2D6:* Appropriate monitoring is recommended and dose adjustment may be necessary for narrow therapeutic index CYP2D6 substrates.**Adverse Reactions**: Most commonly reported adverse reactions (>2% and > placebo) were hypertension, nasopharyngitis, urinary tract infection and headache.**Use in specific population**: *Pregnancy:* Use only if the benefit to the mother outweighs the potential risk to the fetus. *Nursing Mothers*: OAB-F is not recommended for use in nursing mothers. *Paediatric population*: Safety and effectiveness of OAB-F in paediatric population has not been established. *Geriatric use*: No dosage adjustment necessary for elderly patients. *Patients with End Stage Renal Disease (ESRD) or Patients with Severe Hepatic Impairment:* Not recommended.

MARKETED BY:

Alembic Elena

Prime Corporate Park, 2nd Floor, behind ITC Grand Maratha Sheraton, Sahar Road, Andheri (E), Mumbai – 99.
Tel.: 30611698 Fax: (022) 30611682 Website: www.alembic-india.com