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Diagnosis and Treatment of Overactive Bladder

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1. Introduction

Overactive bladder (OAB) is a disturbance of filling/storage and has been defined by the International Continence Society as "a symptom syndrome consisting of urgency with or without urge urinary incontinence, often associated with urinary frequency and nocturia." (Abrams et al., 2002) OAB has been divided into OAB without urinary incontinence (OAB_{dry}) and OAB with urinary incontinence (OAB_{wet}). The reported prevalence of OAB in women varies between 7.7 and 31.3%, and increases with age. (Irwin et al., 2006a; McGother et al., 2006;Milsom, et al., 2001; Stewart et al., 2003; Wagg et al., 2007)

The symptoms of OAB include urinary urgency, urinary frequency, nocturia, and urinary urge incontinence. These symptoms often remain undetected and undertreated by both the woman and her providers, despite the substantial impact on a woman's quality of life. (Griffiths et al., 2006; Mardon et al., 2006) In a multiethnic survey, only 45 percent of women who reported weekly urinary incontinence sought care for their incontinence symptoms. (Harris et al., 2007) This leaves incontinent women with psychological morbidity and a diminished quality of life. (Irwin et al., 2006b)

2. Etiology

2.1 Normal micturition

The normal micturition cycle includes inhibition and contraction of detrusor smooth muscle, afferent signaling from the urothelium, contraction and relaxation of the smooth and striated sphincter muscles, and the central, peripheral, and autonomic nervous systems.

Urine storage occurs secondary to afferent signals stimulated by bladder filling. These afferent signals activate sympathetic pathways in the hypogastric and pudendal nerves, which lead to contraction of the smooth and striated sphincters, and at the same time inhibit detrusor contraction. In addition, high cortical centers are activated, (Griffiths et al, 2007), and stimulate the storage center in the pons. (Fowler et al, 2008) When further bladder filling leads to increased afferent signaling from the bladder, spinobulbospinal reflex pathways are carried via the pelvic nerve and spinal cord to the pontine micturition center, which activates parasympathetic pathways that cause bladder contraction and inhibit sympathetic and pudendal contraction of the sphincter (Fowler et al, 2008)

For coordinated micturition to occur, parasympathetic stimulation of the detrusor occurs via cholinergic muscarinic receptors. Urethral smooth muscle contraction occurs chiefly by stimulation of alpha-adrenerigic receptors. (Fowler et al, 2008) In addition, a variety of neurotransmitter systems in the urothelial lining of the bladder and in bladder interstitial cells likely play a role in mediating bladder contraction and relaxation via afferent signaling. (Andersson, 2002) This complex interplay results in socially appropriate and effective voiding. Any disruption in this pathway can lead to storage and/or emptying disorders. Bladder overactivity may be related to neurogenic, myogenic, or idiopathic origins.

2.2 OAB etiology

The presumed etiology of OAB is uninhibited bladder contractions, but overactivity is not sufficient to cause incontinence (e.g. OAB_{dry}). In addition, leakage symptoms may be due to factors outside of the lower urinary tract such as failure of compensatory mechanisms in the lower urinary tract (e.g. fascial and muscular urethral support "hammock" that compresses the urethra when there is increased abdominal pressure or when the pelvic muscles are contracted) , and functional impairments in some patients.

2.2.1 Neurogenic etiologies

2.2.1.1 Suprapontine lesions

Patients with suprapontine lesions such as cerebrovascular disease and Parkinson's disease can present with detrusor overactivity. These patients lose voluntary inhibition of micturition most likely secondary to uninhibited detrusor contractions. (Fall, et al, 1989) (Fall, et al, 1995) The cerebral cortex and the basal ganglia are theorized to suppress the micturition reflex. Therefore, damage to the brain results in bladder overactivity by reducing suprapontine inhibition. (Koelbl et al, 2009)

2.2.1.2 Spinal cord lesions

Spinal cord disruption below the level of the pons leads to unsustained and uncoordinated detrusor contractions. (Koelbl et al, 2009) Impairment or loss of bladder sensation usually occurs. Patients with spinal cord lesions above the lumbosacral level lose voluntary and supraspinal control of micturition. Bladder overactivity in these patients is mediated by spinal reflex pathways (deGroat et al, 1993) (Bros & Comarr,1971)

2.2.2 Non-neurogenic etiologies

2.2.2.1 Outflow obstruction

Outflow obstruction is associated with detrusor overactivity. (Koelbl et al, 2009) Up to 50% of patients with symptomatic benign prostatic enlargement exhibit bladder outlet obstruction. (de Nunzio et al, 2003) However, OAB symptoms can occur independently of bladder outlet obstruction. One hypothesis that has been proposed to explain how outflow obstruction causes OAB and detrusor overactivity includes partial denervation.

Denervation injury has been shown to increase detrusor supersensitivity to acetylcholine. (Harrison et al, 1987) This may be the basis of unstable bladder activity. However, it is not clear how denervation develops in patients with outflow obstruction. It is possible that there

is a reduction of blood flow due to increased intravesical pressure during voiding or the increased tissue pressure of hypertrophied bladder wall during filling. (Azadzoi et al, 1996) (Greenland & Brading, 2001)

2.2.2.2 Aging

The prevalence of OAB in both men and women increases with age. In addition, storage symptom scores increase with age while bladder compliance decreases. (Koelbl et al, 2009) This implies that bladder function in both sexes has age related alterations. (Araki et al, 2003) There can be difficulty however, in determining in the elderly, the difference between neurogenic and non-neurogenic causes.

2.2.2.3 Estrogen deficiency

Menopause and estrogen deficiency have been implicated in the etiology of OAB symptoms. (Koelbl et al, 2009) Estrogen receptors (ERs) have been identified in the bladder and urethra. (Blakeman et al, 2000) The effect estrogen has on bladder contractility has yet to be elucidated.

However, it has been shown that estrogen replacement therapy can significantly improve the symptoms of frequency, urgency and urge incontinence. (Eriksen & Rasmussen,1992) In addition, a metaanalysis of the effects of estrogen therapy on symptoms of OAB in postmenopausal women showed that estrogen therapy was associated with significant improvements in all symptoms of OAB. (Cardoza et al, 2004b) Thus it appears that menopause plays role in the development of bladder overactivity and OAB symptoms in women.

2.2.3 Idiopathic etiologies

Idiopathic detrusor overactivity is a diagnosis of exclusion of all other known causes. Mechanisms that have been proposed for idiopathic detrusor overactivity include myogenic, urothelial and muscarinic.

2.2.3.1 Myogenic

Mills et al, noted that denervation is consistently found in detrusor biopsies from patients with non-neurogenic detrusor overactivity. (Mills et al, 2000) They hypothesize that partial denervation of the detrusor alters the properties of smooth muscle, which leads to increased excitability and increased coupling between cells. Thus, myogenic changes in the bladder increase contractility locally.

2.2.3.2 Urothelial

Another mechanism that has garnered interest in idiopathic detrusor overactivity is the roles of the urothelium and suburothelial myofibroblasts in afferent activation. The C-fiber afferents have endings in the suburothelial layer of the bladder wall, and may reach the urothelium. (Koelbl et al, 2009) Upon bladder distention ATP has been shown to be released from the urothelium. (Ferguson et al, 1997) ATP receptors on afferent nerve terminals are stimulated by ATP release to evoke a neural discharge. It has been proposed that there is up-regulation of the afferent activation mechanisms(eg. an increased generation/release of ATP increased sensitivity of afferent nerves to mediators, increased number of afferent nerves) can cause the symptoms of OAB. (Koelbl et al, 2009)

2.2.3.3 Muscarinic

As stated above, muscarinic receptors play a significant role in OAB. ATP, Acetylcholine (Ach) and other "signaling molecules, interact with the afferent nerve fibers under the urothelium. Bladder distention presumably causes release of Ach (and other molecules) to stimulate muscarinic receptors on myofibroblasts(predominantly M2). (Mansfield et al 2005) It appears that an increase in Ach release from the urothelium and/or upregulation of muscarinic receptors in the urothelium as well as in suburothelial myofibroblasts may increase afferent nerve activity and contribute to the development of detrusor overactivity. (Koelbl et al, 2009)

3. Clinical presentation

Women with OAB may experience urinary urgency at inconvenient and unpredictable times. Urgency is the complaint of a sudden compelling desire to pass urine which is difficult to defer. In addition, patients may experience increased 24-hour frequency defined as the total number of daytime voids and episodes of nocturia during a specified 24 hours period. Daytime frequency is defined as 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. Both frequency and urgency may occur and urine leakage may occur prior to reaching a toilet. These symptoms interfere with work, activities of daily life, intimacy, and sexual function, and they can also cause embarrassment and diminished self-esteem. (Shaw & Burrows, 2011) Many patients with OAB have symptoms that wake them up at night. Nocturia is the complaint that the individual has to wake at night one or more times to void.

4. Diagnosis

The presumptive diagnosis of OAB can usually be made in the primary care provider's office. Patients who present with the symptoms of urinary urgency and frequency can be evaluated utilizing standardized questionnaires, bladder diaries, a thorough history and physical examination, and simple laboratory tests. Those patients with more complex presentations may require urodynamic studies to confirm the diagnosis of OAB or detrusor overactivity.

4.1 Symptom and quality of life questionnaires

One of the most important aspects of the patient's history is to establish the impact of symptoms on their lives. This will guide the rest of the evaluation and subsequent treatment decisions. Most of the currently used symptom scales focus on patient-perceived frequency of symptoms and how much bother the symptoms cause. (Basra et al., 2007; Coyne et al., 2005a; Coyne et al., 2005b) Some newer validated scales have been developed which target more specific aspects of OAB. One of these, the OAB symptom score, is a 7-item questionnaire that records all the symptoms of OAB using consistent terminology. (Blaivas et al., 2007) Additionally, the International Continence Society (ICS) have established questionnaires (eg International Consultation on Incontinence Modular Questionnaire (ICIQ)) (Abrams et al, 2009))

4.2 Bladder diaries

Bladder diaries are an excellent tool that can be utilized to assess the frequency of daytime and nighttime voiding, as well as the timing of incontinence episodes and pad usage. Recently, bladder diaries have been developed that reliably assess the rate and severity of urinary urgency and are readily available. (Abrams et al, 2009) Despite some limitations, bladder diaries do provide a baseline with which to compare treatment efficacy.

4.3 History

A thorough history should inquire about the onset, duration, severity, and bother of lower urinary tract symptoms. In addition, a medical, surgical, gynecological, and obstetrical history should be obtained. Inquire about current medications which affect bladder function, particularly diuretics, alcohol, caffeine, narcotics, and calcium channel blockers.

4.4 Physical Examination

The physical examination should be focused on the abdominal and genitourinary examinations. The pelvic examination is used to evaluate the strength of the muscles of the pelvic floor and to assess for pelvic organ prolapse, urethral mobility, and stress urinary incontinence. The rectal examination is used to assess for any masses and to evaluate for constipation and anal tone. A simple, focused neurologic examination to evaluate pelvic reflexes, innervation of the lower extremities, and the patient's mental status completes the physical examination.

4.5 Urinalysis

Because some patients who present with acute symptoms of frequency and urgency have a urinary tract infection, a urinalysis (UA) is performed. In addition a UA will detect hematuria or glucosuria.

4.6 Postvoid residual

A post-void residual (PVR) is performed as a rough evaluation of as a measurement of the efficiency of evacuation of the bladder. This can be measured by bladder ultrasonography or post-void catheterization. Although there is no universally accepted definition of an abnormally elevated PVR, a high post-void residual (greater than 100 cc) may be cause for further, more complex testing. In addition, patients with high PVR's are at high risk for urinary retention, especially when anticholinergic medications are prescribed.

4.7 Urodynamic studies

Urodynamic studies can provide additional insight into bladder pathophysiology and can be a key to making the diagnosis of OAB and destrusor overactivity. Urodynamic studies are a series of clinical tests, such as flow studies, filling cystometry, pressure-flow studies and/or urethral function measurements. These can be combined with electromyography (EMG) recording and/or imaging by either X-rays or ultrasound. (Abrams et al, 2009)

The goal of urodynamic studies is to reproduce the symptom(s) of the patient under controlled and measurable conditions. According to the 4th International Consultation on Continence (Abrams et al, 2009) the role of urodynamic studies can be:

- To identify or to rule out factors contributing to the lower urinary tract(LUT) dysfunction To obtain information about other aspects of LUT dysfunction
- To predict the consequences of LUT dysfunction for the upper urinary tract
- To predict the outcome, including undesirable side effects, of a contemplated treatment
- To confirm the effects of intervention or understand the mode of action of a particular type of treatment
- To understand the reasons for failure of previous treatments for urinary incontinence, or for LUT dysfunction in general.

In addition to recommending the role of urodynamic studies, The International Continence Society (ICS) has provided standards for urodynamic terminology and techniques (Abrams, 2002) For example, urodynamic detrusor overactivity is defined by the ICS as "Loss of urine as a result incontinence of involuntary detrusor activity during the storage phase of urodynamic testing.

Following is a brief description of the most commonly used urodynamic studies.

4.7.1 Uroflowometry

Uroflowometry is a non-invasive measurement of urine flow rate. The patient urinates into a flow meter in private. (Schafer,2002) The flow rate is measured and displayed graphically. The volume voided, shape of the curve and the maximum flow rate are automatically graphed. These parameters determine if the patient is emptying their bladder normally. When an abnormal recording is obtained, it is best to repeat the assessment for reproducibility.

4.7.2 Filling cystometry

Filling cystometry is an invasive measurement of the pressure inside the bladder to assess its storage capabilities. It involves placing a pressure sensor into the bladder and another pressure sensor rectally or vaginally to measure abdominal pressure. A computer subtracts the abdominal pressure from the bladder pressure to provide the clinician with a graphic representation of pressure changes due to the true detrusor muscle. The bladder is usually filled with normal saline through the transurethral filling channel of a dual lumen catheter. The filling rate is usually controlled by a computer and the intravesical abdominal and detrusor pressure are monitored graphically. The storage ability of the bladder is assessed and presented graphically in terms of the volumes required to elicit various bladder sensations from the patient, its capacity, its compliance and its stability. The filling (storage) phase of cystometry is also the only method of demonstrating urodynamic stress incontinence (USI). (Abrams et al, 2009)

4.7.3 Pressure-flow studies (Voiding cystometry)

Voiding cystometry is a measurement of the mechanics of micturition. Generally this study is performed after bladder filling during cystometry is complete. While monitoring

intravesical, abdominal and detrusor pressures, the patient is allowed to void and empties their bladder on a flow meter. Measurement of both flow rate and pressure allows voiding to be assessed. In patients whose bladder emptying is poor, it may determine if poor flow is due to outflow obstruction or poor detrusor contractility.

4.7.4 Urethral pressure profilometry

Urethral pressure profilometry is a test that measures the urethra's ability to maintain pressure along its length. This test is performed by placing a pressure sensor transurethrally into the bladder and usually withdrawing it along the urethra by a mechanical puller at a constant rate. The pressure along the length of the urethra is measured and graphically represented. The maximum pressure measured in the urethra gives an indication of the closure function of the urethra.

4.7.5 Abdominal leak point pressure

Similar to urethral pressure profilometry, abdominal leak point pressure is used as a measure of the urethra's ability to act as a valve to store urine. Intravesical or abdominal pressure is assessed while the patient is asked to increase their abdominal pressure by valsalva or by coughing. The abdominal pressure at which the patient leaks urine gives a measure of the closure pressure of the urethra. The greater the pressure required to produce leakage, the better the closure function of the urethra.

5. Management

The most commonly used measure of urinary incontinence (UI) treatment efficacy is a reduction in urinary incontinence episodes. Generally, this is recorded as the reduction in mean number of daily episodes, percent reduction from baseline, or reduction in leakage volume. Other outcome measures commonly used for OAB are urinary frequency (total number of daytime and nighttime voids) and frequency of urgency symptoms (with or without leakage). Cure is usually defined as complete absence of urinary incontinence. (Abrams, 2009)

One of the most important measures from the patient's perspective is quality of life. In the literature, many investigations measure patient perception of improvement of OAB, general satisfaction questions, and urinary incontinence-specific quality of life measures. The ICS recommends using patient reported outcome questionnaires that have been rigorously evaluated. (Koelbl et al, 2009)

5.1 Conservative therapies

Once the diagnosis of OAB has been made, the combination of dietary and lifestyle modification, bladder training, pelvic floor muscle training (PFMT), and biofeedback should be recommended as the initial intervention for OAB. (Burgio, 2002) The Agency for Health Care Policy and Research as well as the Third International Consultation on Incontinence recommends behavioral therapy as first-line therapy. (Wilson et al., 2005) The advantages of behavioral methods include avoidance of surgery, improved central control of bladder function and no adverse drug reactions.

5.1.1 Dietary and lifestyle modification

A common sense approach to the treatment of patients with OAB should include counseling patients on dietary and lifestyle modification that may improve their symptoms and quality of life. In general, patients should increase awareness of amounts and types of fluids consumed, especially as it relates to their symptoms. Although not well studied some foods and beverages are believe to increase detrusor activity and symptoms of OAB. The authors recommend that patient's begin to eliminate one food or beverage at a time from the following list:

- Beverages
  - Alcoholic
  - Caffeinated (Coffee, Tea)
  - Carbonated
- Foods
  - Tomatoes and tomato-based products
  - Spicy foods
  - Citrus juice and fruits
  - Artificial sweeteners
  - Chocolate
  - Corn syrup
  - Sugar
  - Honey

In one study patients with caffeine intake > 400 mg/day were shown to be 2.4 times more likely to have detrusor overactivity. (Arya, et al., 2000) In addition, limiting fluid intake has been shown to reduce frequency and urgency as well as improve quality of life in patients with OAB. (Milne, 2008 and Swithinbank et al., 2005)

Although weight loss is a good lifestyle modification, in general, it has been shown to significantly improve only stress urinary incontinence symptoms, but not OAB symptoms. A large randomized trial of overweight and obese women with urinary incontinence symptoms underwent an intensive 6 month weight loss program compared to a group with a structured education program. (Subak et al., 2009) Mean weight loss was 8 percent (7.8 kg) and 1.6 percent (1.5 kg) in the intervention and control groups, respectively. The authors found that weekly incontinence episodes decreased by 47 percent in the intervention group compared to only 28 percent in the control group. Of note, is that these patients had a significant decrease in stress incontinence, but not urge incontinence episodes.

5.1.2 Bladder retraining

Bladder training involves patient education and scheduled voiding in which the voiding interval is progressively increased. This method is based upon frequent voluntary voiding which keeps the bladder volume low and training the central nervous system on pelvic floor musculature to inhibit urgency. Utilizing the patient's bladder diary, the initial frequency of timed voiding is based on the smallest time interval between voids. The goals of bladder training are to normalize urinary frequency, to improve control over bladder urgency, to increase bladder capacity, to decrease incontinence episodes, to prolong voiding intervals,

and to improve the patient's confidence in bladder control. It is safe and may be beneficial. (Wallace et al., 2004) Bladder training requires compliant and motivated patients and may not be suitable for those with cognitive impairment. It can be time-consuming and is primarily effective during waking hours. (Ouslander et al., 2001)

Patients can be instructed to follow the steps listed below for bladder training :(Modified from DuBeau, 2011):

- Go to the toilet and try to pass urine every two hours while you are awake.
  - You do not have to get up during the night!
- You must try to pass urine whether you feel the need or not
- You must try to pass urine even if you have just been incontinent.
- If you get a strong urge to go to the bathroom before your scheduled time:
  - Stop, don't run to the bathroom!
  - Stand still or sit down if you can.
  - RELAX. Take a deep breath and let it out slowly.
  - Concentrate on making the urge decrease or even go away, anyway you can.
  - When you feel in control of your bladder, walk slowly to the bathroom, and then go.
- Keep this schedule until you can go two days without urine leakage.
  - Then, increase the time between scheduled trips to the toilet by one hour
  - When you can go two days without urine leakage, extend the time between trips again.
- Keep this up until you can go four hours between trips to the toilet, or until you are comfortable.
  - This may take several weeks.
  - DON'T GET DISCOURAGED! Bladder training takes time and effort, but it is an effective way to get rid of incontinence without medication or surgery

A review in 2009 found that bladder training may be helpful for the treatment of urinary incontinence, but definitive research is needed to support that conclusion. (Wallace et al., 2004) However, there is very little downside to this therapy.

5.1.3 Pelvic floor muscle training (PFMT)

PFMT involves exercises designed to improve the function of the pelvic floor muscles. Using PFMT to treat OAB is based on the theory that contraction of the levator ani muscles can reflexively inhibit contraction of the detrusor muscle. PFMT is defined as any program of repeated voluntary pelvic floor muscle contractions (VPFMC) taught by a trained healthcare professional. (Wilson et al., 2005) Patients are taught to squeeze the pelvic floor with three sets of 8 to 12 slow velocity contractions held for six to eight seconds each. These exercises should be performed at least three or four times a week and continued for at least 15 to 20 weeks. (Hay-Smith et al., 2009)

There is increasing evidence to support the use of PFMT for OAB. Patients with detrusor overactivity who completed a PFMT program experienced a clinically and statistically significant reduction in daily UI episodes. (Ba & Berghmans, 2000 and Nygaard et al., 1996) These investigators also reported a significant decrease in urge score. This urge score was

defined as the frequency of leakage (0 = never to 4 = always) during 9 activities that can trigger urge incontinence.

5.1.4 Weighted vaginal cones

Patients may have additional improvement in learning to appropriately do PFMT with the use of vaginal weighted cones. These cones are inserted in the vagina by the patient and she learns to contract the pelvic floor muscles to hold the cone in place.

5.1.5 Biofeedback

Biofeedback is used to teach patients how to control normal physiologic responses of the bladder and pelvic floor muscles that mediate urinary incontinence. Biofeedback for OAB consists of bladder-pressure biofeedback as well as the pelvic floor's muscular activity feedback. (Burgio et al., 1985)

5.1.6 Limitations of behavioral therapy

Behavioral therapy requires the active participation of motivated patients and a practitioner well-trained in behavioral therapy. Behavioral therapy does not cause permanent changes in bladder function; therefore, regular adherence and long-term compliance are needed for effectiveness.

5.2 Pharmacological agents

Traditionally, drug therapy is commenced at the same time as behavioral therapy. Drug treatment plays an important role in the management of women with OAB, although many drugs currently in use have not been subjected to controlled clinical trials in the treatment of OAB. From a review of the literature, it is clear that there is no ideal drug. (Hay-Smith et al., 2005) Current pharmacological approaches to improving the treatment of OAB include delayed release formulations of existing oral agents, new pharmaceutical agents with greater specificity/selectivity, and alternative routes of administration. New generation pharmacological treatments provide better or comparable efficacy with fewer adverse drug events. (Shaw & Burrows, 2011)

5.2.1 Antimuscarinic (anticholinergic) drugs

There are many different antimuscarinic compounds licensed for use for patients with OAB. Oxybutynin was the first drug of this class used specifically to treat the symptoms of OAB. This class of drugs has been considered the “gold standard” in the treatment of OAB for many years. However, there is little or no evidence to help clinicians choose between particular anticholinergic drugs. To add to the difficulty with studying this class of drugs, compliance with antimuscarinics is generally poor. (Brubaker et al., 2010)

Traditionally, it was thought that these drugs act by blocking the muscarinic receptors on the detrusor muscle. This resulted in decreased bladder contractions and thus reduced the symptoms of OAB. However, it appears that antimuscarinic drugs act primarily during the storage phase of the micturition cycle, decreasing urgency and increasing bladder capacity.

During this phase, there is normally no parasympathetic input to the LUT. (Abrams & Andersson, 2007)

A recent Cochrane review assessed the various anticholinergics available for the treatment of OAB in adults. The conclusions of this review were when the prescribing choice is between oral immediate-release oxybutynin and tolterodine, tolterodine might be preferred due to a reduced risk of dry mouth. In addition, they concluded that if extended-release preparations of either drug are available, they would be preferred to the immediate-release preparations because of the decreased risk of dry mouth and better compliance. There were insufficient data from trials of other anticholinergic drugs to draw any conclusions. (Hay-Smith et al., 2005) The most commonly prescribed anticholinergic drugs and their dosages in the treatment of OAB are listed in Table 1. (Shaw & Burrows, 2011)

5.2.1.1 Oxybutynin

As mentioned above, oxybutynin was the first anticholinergic widely used for the treatment of OAB. It is an anticholinergic agent that has antimuscarinic, antispasmodic, and potential local anesthetic effects. Oxybutynin has been shown to have a high affinity for the M1 & M3 receptors and much less affinity for the M2 receptor. (Hughes et al., 1992 and Nilvebrant & Sparf, 1986) It is available in immediate release (IR), extended release (ER), transdermal patch and topical gel formulations. In general, the efficacy is similar for all formulations. The initial dosage for IR is 2.5 mg two to three times daily, followed by titration as needed up to 20 mg/day in divided doses. The ER formulation is started at 5 mg once daily and titrated up to 20 to 30 mg once daily.

The transdermal patch (equivalent to 3.9 mg/day) applied to the abdomen, hip, or buttock is changed twice a week. The topical 10% gel is applied as 1 gm (approximately 1 mL) daily to the thigh, abdomen, upper arm, or shoulder. Currently, oxybutynin IR and ER are available as generic formulation in the United States. Oxybutynin IR is associated with high rates of anticholinergic adverse effects. Dry mouth is a particularly bothersome side effect for patients that can limit therapy with oxybutynin IR. This side affect is less frequent with the ER and transdermal preparations (Anderson et al., 1999; Davila et al., 2001; Versi et al., 2000) Irritation and pruritus at the application site has been reported in approximately 15 percent of patients using transdermal oxybutynin and 5 percent using the topical gel. (Dmochowski et al., 2002)

5.2.1.2 Tolterodine

Tolterodine has been shown to be a competitive muscarinic receptor antagonist with some selectivity for bladder muscarinic receptors [59]. It is available in immediate- and extended-release forms. Tolterodine is administered at 1 to 2 mg twice a day for the IR preparation or 2 to 4 mg per day using the ER preparation. It has similar efficacy when compared to other antimuscarinics. Both formulations have shown efficacy for symptoms of OAB in a large study population (Choo et al., 2008).

One of the few “head to head” studies between anticholinergic drugs was The STAR trial. In this study the investigators directly compared solifenacin (discussed below) at a flexible 5 or 10 mg once daily dose with tolterodine extended release 4 mg once daily in a randomized

controlled trial. (Chapple et al., 2005) The authors found that the flexible dose of solifenacin showed marked advantages over the single dose of tolterodine extended release. In a reanalysis comparing only the patients in the trial taking solifenacin 5 mg once daily with the patients in the tolterodine arm the authors found a more modest benefit. (Chapple et al., 2007) Solifenacin 5 mg once daily was superior for incontinence episodes and pad usage, but showed no difference in urge incontinence or dryness rates. Notably in both analyses, the main advantage for solifenacin was minimizing rates of dry mouth and constipation. However, there were slightly more withdrawals due to adverse events in the solifenacin group.

5.2.1.3 Solifenacin

Solifenacin is an antimuscarinic agent has potent selectivity for the M3 over the M2 receptor. (Chapple et al., 2006) In addition it has a higher affinity for the M3 receptor in smooth muscle than it does for the M3 receptor in the salivary gland. (Chapple et al., 2006). This M3 selectivity provides for an improved side effect profile. Solifenacin is administered at 5-10 mg daily for the treatment of OAB.

It has been proven efficacious in multiple trials in patients with OAB. (Cardozo et al., 2004; Cardozo et al., 2008; Chapple, 2005) Another recent study confirmed that solifenacin was significantly more effective in reducing the mean number of severe urgency episodes with or without incontinence per 24 hours, improved urgency symptoms and was well tolerated. Additionally, no cognitive impairment has been associated with this drug. (Kay et al., 2006)

5.2.1.4 Trospium chloride

Trospium chloride is a quaternary ammonium compound that is nonselective for the muscarinic receptor. It also has smooth muscle relaxant qualities. (Staskin et al., 2007) Trospium chloride is available in an IR formulation given 20 mg twice daily or an ER formula administered 60 mg daily. The uniqueness of this antimuscarinic is that it is renally cleared. Care should be used in the elderly and patients with renal impairment. The initial dosing in these patients she be the IR formulation 20 mg once daily. The ER formulation should not be used in patients with severe renal impairment. Because of poor bioavailability, trospium chloride must be taken on an empty stomach.

When compared to placebo, trospium chloride showed a greater decrease in the number of daily episodes of incontinence than patients who received placebo (from a mean of 2.9 to 1.0 with trospium and 1.6 with placebo). (Zinner et al., 2004) Side effects in the trospium chloride group included dry mouth (20 percent) and constipation (11 percent).

In a randomized trial utilizing the ER formulation (60 mg once daily) for patients with severe urge incontinence, patients' incontinence episodes decreased significantly compared to placebo. Adverse events were lower than reported for immediate-release trospium chloride (dry mouth 13 percent, constipation 8 percent). (Dmochowski et al., 2008)

5.2.1.5 Fesoterodine

Fesoterodine is given at a starting dose of 4 mg once daily, which can be increased to 8 mg. As with most of the anticholinergic drugs, the most common side effects are dry mouth and constipation.

Fesoterodine is metabolized to 5-hydroxymethyl tolterodine, (the active metabolite of tolterodine).

5.2.1.6 Darifenacin

Similar to solifenacin, the newer antimuscarinic drug darifenacin is more selective for M-3 muscarinic receptors in the bladder. Drifenacin is administered 7.5 mg daily and can be increased to 15 mg daily. In a randomized trial of darifenacin versus placebo, median incontinence episodes were show to significantly decrease with darifenacin. (Zinner et al., 2006) However, dry mouth and constipation rates were similar when compared to other anticholinergics (29% dry mouth and 18% constipation).

As noted above, the most common side effects associated with darifenacin are mild to moderate dry mouth and constipation. This drug has been studied in patients who were dissatisfied with prior OAB treatment with oxybutynin ER or tolterodine ER. The authors found significant improvements in OAB symptoms with darifenacin. (Zinner et al., 2008) Additionally, long-term studies have shown persistence of continuation with darifenacin therapy and well-maintained treatment benefits (over 2 years in duration). (Haab et al., 2006 & Hill et al., 2007)

Because of its' selectivity for the M3 receptor darifenacin minimizes the risk of side effects due to blockade of other muscarinic subtypes, such as M1 mediated cognitive impairment. (Foote et al., 2005) This is important in relation to the treatment of elderly populations who may be more susceptible to cognitive impairment and CNS effects.

Generic name	Brand Name	Dosage & Administration
Darifenacin hydrombromide	Enablex	7.5 to 15 mg daily
Fesoterodine	Toviaz	4 mg daily, can be increased to 8 mg daily
Oxybutynin extended release	Ditropan XL	5 mg daily, titrate up to 20-30 mg daily
Oxybutynin gel	Gelnique	Topical 10% gel applied as 1 g daily to thigh, abdomen, upper arm or shoulder
Oxybutynin immediate release	Ditropan	2.5 mg 2-3 times daily, followed by titration as needed u to 20 mg/d in divided doses
Oxybutynin transdermal	Oxytrol	Applied to abdomen, hip or buttock and changed twice per week (equivalent to 3.9 mg/d)
Solifenacin succinate	Vesicare	5-10 mg daily
Tolterodine tartrate extended release	Detrol LA	2-4 mg daily
Tolterodine tartrate immediate release	Detrol	1-2 mg twice daily
Trospium chloride extended release	Sanctura	60 mg daily
Trospium chloride immediate release	Sanctura	20 mg twice daily

Table 1. Commonly prescribed anticholinergic drugs for treatment of OAB

5.2.2 Antidepressants

5.2.2.1 Duloxetine

Duloxetine is a serotonin noradrenaline re-uptake inhibitor that is approved by the Food and Drug Administration (FDA) for depression, but not for urinary incontinence. The mechanism of action is to significantly increase sphincteric muscle activity during the filling/storage phase of micturition. Although not approved for use in patients with OAB symptoms alone, it may have some efficacy. Steers et al (Steers et al., 2007) randomized 306 women to placebo or duloxetine over 12 weeks. Duloxetine showed significant benefit in 24-hour urinary frequency and incontinence episodes. It also improved condition-specific quality of life measures. However, no significant increase was observed in mean voided volume, suggesting that the benefits were mediated through an effect at the urethral rhabdosphincter, rather than any direct effect on detrusor contractility. Thus, duloxetine may be considered as an option for patients who cannot tolerate antimuscarinic drugs. However, duloxetine's primary efficacy is in the treatment of stress urinary incontinence.

5.2.2.2 Imipramine

Imipramine, an antidepressant, is the only drug in this category that has been widely used to treat the symptoms of OAB. It has multiple pharmacological effects, including systemic antimuscarinic actions and blockade of the reuptake of serotonin and noradrenaline, but its mode of action in the treatment of OAB is not clear. (Hunsballe & Djurhuus, 2001) Imipramine has shown a favorable therapeutic effect in the treatment of nocturnal enuresis in children with a success rate of 10–70% in controlled trials. (Glazener et al., 2003; Hunsballe & Djurhuus, 2001) However, there are no good quality randomized trials that prove the efficacy of imipramine in the treatment of OAB.

5.2.3 Intravesical botulinum toxin

Botulinum toxin is a neurotoxin that inhibits the release of acetylcholine from presynaptic cholinergic nerve endings. This inhibition results in a localized reversible chemical denervation, with decreased detrusor contractility. Although it is currently not FDA-approved for the treatment of OAB, it shows promise as an addition to the treatment arsenal. The most likely place for its use is for patients who fail oral therapies. Current data primarily address only patients with refractory detrusor overactivity. In the most recent Cochrane review, randomized trials of intravesical botulinum versus placebo reported results favoring botulinum toxin. (Duthie et al., 2007) The authors noted that there was significant improvement in incontinence episodes, bladder capacity, maximum detrusor pressure and quality of life. They concluded "Botulinum toxin injections into the bladder appeared to give few side effects or complications, but there were no long-term follow-up studies, and there could be rare side effects that have not been discovered yet." (Duthie et al., 2007)

As stated above, many questions remain regarding its use, including the optimal dose and site of injection, the appropriate population, and long-term safety. To address this issue, Schurch et al (Schurch et al., 2007) randomized 59 patients with neurogenic detrusor overactivity to intravesical botulinum A (200 or 300 U) or placebo. These investigators noted significant improvements when compared to placebo using the Incontinence Quality of Life

Questionnaire. They did not discover clear differences between the two doses. Intravesical botulinum toxin has a variable duration of action, with loss of efficacy typically seen within one year. (Reitz et al., 2007) Based upon this limited data, it appears that there may be a role for the use of intravesical botulinum for patients with OAB, especially when other therapies fail. Finally, one of the bothersome adverse effects is urinary retention which can last up to three months after one injection. This, the clinician must have considerable knowledge and skill in the judicious use of botulinum toxin.

In a recent literature review (Anger et al, 2010) the authors systematically reviewed the efficacy and safety of botulinum toxin in the management of overactive bladder. Based upon this review of three small randomized placebo controlled trials they found that patients treated with botulinum toxin-A had 3.88 fewer incontinence episodes per day (95% CI -6.15, -1.62). Patients also noted significant improvements in quality of life compared with placebo. In addition they found a 9-fold increased odds of increased post-void residual after botulinum toxin-A compared with placebo (8.55; 95% CI 3.22, 22.71). They concluded that "intravesical injection of botulinum toxin resulted in improvement in medication refractory overactive bladder symptoms".

5.2.4 Combination therapies

Since most patients do not achieve complete continence with behavioral therapy or anticholinergic therapies alone, many clinicians combine these two in the treatment of OAB. A combination of anticholinergic agents and behavioral interventions have been shown to be safe and effective in many studies. (Fantl et al., 1996; Gormley, 2002; Milne & Moore, 2006) Side affect profiles of most of the drugs used for OAB make long term adherence to therapy difficult.

In a large study, Mattiasson et al (Mattiasson et al., 2003) showed additional benefit from bladder retraining when compared with tolterodine alone. Additionally, 76% of the patients on tolterodine and behavioral therapy noted improvement in their bladder symptoms compared to baseline as compared with 71% in the tolterodine group (Mattiasson et al., 2003)

Combination therapy has been shown to be associated with significantly fewer incontinent episodes, an improved quality of life, and greater treatment satisfaction when compared to non-pharmacologic intervention alone or drug treatment alone. (Wyman et al., 1998) However, the authors found that the effects of each of the interventions were similar 3 months after treatment. They concluded that the nature of the treatment may not be as important as having a structured intervention program that includes education, counseling, and frequent monitoring of the treatment. (Wyman et al., 1998)

Finally, Chancellor et al (Chancellor et al., 2008), in a more recent trial, compared the benefits of anticholinergic therapy alone against a combination of anticholinergic and behavioral therapy in 395 patients in a randomized controlled trial of flexible dose darifenacin (7.5 mg/day increased to 15 mg/day if required), with or without additional advice about dietary modification, timed voiding/bladder retraining, and pelvic floor training. No significant differences were observed between groups in OAB symptoms.

5.3 Neuromodulation

Neuromodulation can be utilized to increase pelvic muscle contraction and decrease detrusor contractions. The use of neuromodulation is assumes that OAB results from an imbalance of inhibitory and excitatory control systems of the detrusor that leads to the symptoms of OAB during the filling phase. (Fall and Lindstrom ,1991) Neuromodulation is gaining popularity because it bridges the gap between conservative treatments and highly invasive options. Currently, the methods used include sacral nerve modulation (SNM) via surgically implanted electrodes and other newer methods that deliver percutaneous stimulation of the peripheral tibial nerve.

The exact mechanism of action for neuromodulation is not well understood. However, many theories have been proposed as follows. (Al-Shaiji et al, 2011)

- Sensory input through the pudendal nerve has been shown to inhibit detrusor activity. Pudendal nerve stimulation and enhancement of external sphincter tone may serve to control bladder overactivity and facilitate urine storage. (Vodusek et al, 1986)
- The bladder responds to neural stimulation initially with rapid contraction. This is then followed by slow, longer-lasting relaxation. With recurrent, repetitive electrical stimulation, there is a downregulation of the bladder's response, thus reducing the detrusor muscle overactivity. (Appell & Boone, 2007)
- Stimulation of afferent sacral nerves in the pelvis or lower extremities has been shown to increase the inhibitory stimuli to the efferent pelvic nerve thus reducing detrusor contractility. (Fall & Lindstrom, 1991)
- Neuromodulation affects the "neuroaxis" at various levels and restores the balance between excitatory and inhibitory regulation at various locations within the peripheral and central nervous system. (Van Der Pal, 2006)

5.3.1 Noninvasive electrical stimulation

There are several devices on the market to provide noninvasive electrical stimulation to the pelvic floor. The removable device is placed in the. Its mechanism of action in the treatment of OAB is thought to be secondary to reflex inhibition of the detrusor muscle by stimulation of the pudendal nerve. There is some evidence that this therapy has some efficacy in the treatment of OAB. (Berghmans et al., 2000; Goode et al., 2003)

5.3.2 Sacral neuromodulation (SNM)

SNM uses mild electrical pulses to stimulate the sacral nerves that innervate the pelvic floor and lower urinary tract. InterStimTM therapy was developed by Medtronic (Minneapolis, Minn, USA) for use in humans. This technology utilizes an implanted unilateral lead stimulating the S3 nerve root. This electrode is attached to a small pacemaker placed within a subdermal pocket in the buttock region. It is FDA approved for refractory urge incontinence, refractory urgency frequency, and idiopathic nonobstructive urinary retention. "Off-label uses of the technology include for treatment of interstitial cystitis and pelvic pain syndrome. (Al-Shaiji et al, 2011)

Implantation of the device usually proceeds in 2 steps: a test phase and implantation or lead removal based on test response. The initial test phase can be performed in the office or

operating room allowing for placement of the lead with a test period of 1 to 2 weeks; full implantation can be performed under local or general anesthesia. Response is objectively evaluated by pre- and postvoiding diaries assessing various urinary parameters.

The test phase of the procedure consists of implantation of tined quadripolar leads, under intravenous (IV) sedation, local anaesthesia, or general anaesthesia. Under fluoroscopy with a C-arm the right or left S3 foramen is identified and the permanent tined lead is passed through the foramen needle. The lead is then tested for a response. Correct placement in the S3 foramina includes bellows contraction of the pelvic floor and plantar flexion of the great toe. Once the appropriate side and position is selected, the lead is connected to an external pulse generator and taped to the skin surface. A 7- to 14-day home test period is used to determine which patients meet criteria to have the IPG implanted. Patients who respond favorably and demonstrate a 50% symptom improvement from baseline have the permanent generator implanted. (Al-Shaiji et al, 2011)

The most common adverse events include lead migration, implant site pain, bowel dysfunction, and infection. Infection usually resolves with antibiotics and the lead adverse events can usually be corrected by reprogramming, reinforcing the lead, or inserting a new lead contralaterally.

There is now convincing evidence for the success of SNM for refractory OAB. Several studies including RCTs and long-term observational studies reported fair clinical response between 64 and 88% of all patients (Leong et al, 2010).

5.3.3 Percutaneous stimulation of the tibial nerve

In addition, percutaneous stimulation of the tibial nerve (PTNS) has shown promise in the treatment of patients with refractory urge incontinence. PTNS is a minimally invasive, office-based procedure that involves percutaneous placement of a 34-gauge (ga) needle over the medial malleolus of the ankle to provide stimulation of the posterior tibial nerve. The procedure is repeated in 30-minute treatment sessions over a period of 12 weeks. PTNS in patients with OAB has been shown to significantly reduce in symptoms and improvement in health-related quality of life. (Yoong et al, 2010) However, one multicenter randomized trial of 100 patients with OAB symptoms did not show a reduced rate of urinary frequency when PTNS was compared to tolterodine extended release, 4mg daily. (Peters, 2009)

5.4 Surgery

In general most patients with OAB symptoms can be treated with medical and behavioral therapies. Generally, augmentation cystoplasty is only considered when patients have small volume bladders and are debilitated by their symptoms.

5.4.1 Augmentation cystoplasty

Augmentation cystoplasty (AC) is a surgery where a portion of the bowel is removed and patched to the bisected bladder. This procedure increases bladder capacity and decreases bladder pressure caused by unstable detrusor contractions. Considered a procedure of last resort, the risks of the surgery include recurrent UTI's, renal or bladder infections, metabolic changes and mucus production. (Khastgir et al., 2003) reviewed outcomes associated with

augmentation cystoplasty. This group emphasized clinical outcomes (e.g. maximum detrusor pressure and bladder volume capacity) and patient symptoms (e.g. incontinence episodes and number of pads). Other outcomes included a questionnaire that measured quality of life, and the evaluation of complications from the surgery.

Using a definition of success as a $\geq$ 50% reduction in symptoms, one group found a 97% success rate for AC. (Blaivas et al., 2005)

5.5 Future therapies

5.5.1 Beta adrenoreceptor agonists

The human detrusor muscle contains B_2 and B_3-adrenoceptors. Both receptors are thought to be involved in detrusor relaxation. Currently, there are a number of [beta] 3-adrenoceptor selective agonists being evaluated as potential treatment for OAB, including YM178 (mirabegron). Chapple et al (Chapple et al., 2008) conducted a clinical trial with mirabegron versus tolterodine and placebo in patients with OAB. Patients in the treatment arm had a statistically significant reduction in mean micturition frequency when compared to placebo. In addition, mirabegron was superior to placebo in regard to mean volume voided per micturition, mean number of incontinence episodes, nocturia episodes, urgency incontinence episodes, and urgency episodes per 24 hours. The drug was well tolerated, and the most commonly reported adverse effects were headache and gastrointestinal adverse effects. Further randomized trials will be needed to prove efficacy.

5.5.2 Centrally acting drugs

5.5.2.1 Tramadol

Many parts of the brain are activated during storage and voiding and there is increasing interest in centrally acting drugs which modulate the micturition reflex. (Andersson & Pehrson, 2003) Tramadol is an analgesic that is a weak μ-receptor agonist; however, it is metabolized to several different compounds, which inhibit serotonin (5-HT) and noradrenaline reuptake. (Grond & Sablotzki, 2004;Safarinejad & Hosseini, 2006) Both μ-receptor agonist and amine reuptake inhibition are useful in the treatment of OAB. In a double-blind, placebo-controlled, randomized study, 76 patients were given 100 mg tramadol sustained release every 12 hours for 12 weeks. Tramadol significantly reduced the number of incontinence periods by 50% per 24 hours. The authors concluded that tramadol provided beneficial clinical and urodynamic effects.

5.5.2.2 Tachykinins

Tachykinins such as substance P, neurokinin A (NKA), and neurokinin B (NKB) may play a role in OAB. Substance P has a specific receptor (NK1) that is expressed in the dorsal horn of the spinal cord and may play an important role in detrusor overactivity. (Grond & Sablotzki, 2004; Safarinejad & Hosseini, 2006)

Aprepitant, an NK1 receptor antagonist, has been shown to significantly improve symptoms of OAB in postmenopausal women with a history of urgency incontinence or mixed incontinence in a small pilot. (Green et al., 2006) Aprepitant significantly decreased the average daily number of micturitions (−1.3 ± 1.9) compared with placebo (−0.4 ± 1.7). The

average daily number of urgency episodes was significantly reduced, as were the average daily number of urgency incontinence and total urinary incontinence episodes. The authors concluded that NK1 receptor antagonism holds promise as a potential treatment approach for OAB.

6. Summary

Overactive bladder (OAB) is a common medical condition, yet often undetected and undertreated despite the substantial impact on a woman's quality of life. The etiology of OAB is unclear, but several mechanisms may interplay and interconnected in contributing to the multi-symptom condition. Despite symptoms that often interfere with work, daily life, intimacy, and also cause embarrassment and diminished self-esteem, less than half of sufferers seek treatment from a licensed provider.

A working clinical diagnosis of OAB can usually be made simply by utilizing proper urinary questionnaires, urinary diaries or a thorough medical history and physical examination. Confirmation of diagnosis is most often achieved via a post-void residual, simply cystometry or multichannel urodynamic testing.

The primary goal of treatment of OAB is simply a reduction in urinary incontinence episodes. First-line therapy for OAB should include conservative options such as timed voiding and alterations in types and amount of fluid intake. Counseling patients on dietary and lifestyle modification will often improve their acute symptoms and decrease the number of voiding episodes per day. Other non surgical first line options include pelvic floor muscle training and/or biofeedback, both of which center around exercises designed to improve the function of the pelvic floor muscles. The primary limitations of behavioral therapy is the required long term patient commitment required for effectiveness.

Antimuscarinic (anticholinergic) drugs are the cornerstone of pharmacological treatment of OAB and provide a favorable efficacy/tolerability/safety profile. These result in decreased bladder contractions and thus reduced the symptoms of OAB. For patients who are not candidates for antimuscarinic (anticholinergic) therapy or have failed previous trials of other medical therapy, noninvasive electrical stimulation to the pelvic floor via neuromodulation may increase pelvic muscle contractions and decrease detrusor contractions . More aggressive nerve modulation and stimulation therapies include, sacral nerve stimulation or peripheral nerve stimulation , which can be considered in patients with refractory urge incontinence. Lastly, surgical options, including augmentation cystoplasty and detrusor myectomy have been developed for those in which all other treatment alternatives have been exhausted.

Lastly, there are promising new receptor-specific medical alternatives emerging and future studies will determine their place in the therapeutic arsenal.

Despite the prevalence of OAB, and the patients' lack of willingness to report their life altering symptoms, screening for OAB should be part of every woman's annual well woman visit. Health care providers need not shy away from urinary incontinence questionnaires, as straightforward diagnosis and OAB treatments are available. Although the primary treatment goal of OAB is the reduction in urinary incontinence episodes, to the patient, the most important measure is quality of life.

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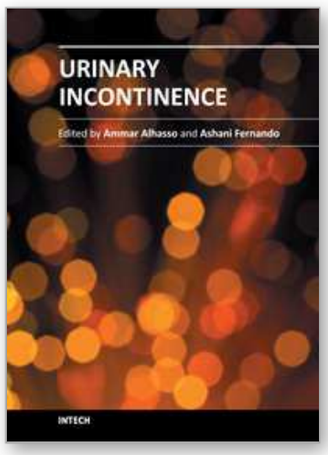

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Management strategies are framed within a multidisciplinary team structure and as such a range of specialists ranging from psychologists, specialist nurses, gynaecologists and urologists author the chapters. There are some novel methods outlined by the authors with their clinical application and utility described in detail, along with exhaustive research on epidemiology, which is particularly relevant in planning for the future.

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