LITERATURE REVIEW

MANAGEMENT OF OVERACTIVE BLADDER

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Abstract

Overactive bladder (OAB) syndrome is a common condition characterized by urinary urgency, with or without urgency incontinence, frequency and nocturia, in the absence of any other pathology. Clinical diagnosis based upon patient self-reported symptoms. Currently there are plenty of treatments available for the management of OAB. Clinical guidelines suggest treatment via a multidisciplinary pathway including behavioural therapy and pharmacotherapy, which can be commenced in primary care, with referral to specialist services in those patients refractory to these treatments. Intradetrusor botulinum A and sacral neuromodulation provide safe and efficacious management of refractory OAB. Percutaneous tibial nerve stimulation and augmentation cystoplasty remain available and efficacious in a select group of patients. Unfortunately, there remains a high rate of patient dissatisfaction and discontinuation in all treatments and thus there remains a need for emerging therapies in the management of OAB.

Keywords: overactive bladder, management

Introduction

Urgency defined by the International Continence Society (ICS) Standardisation of Terminology reports as "a complaint of a sudden, urgent urge to urinate that cannot be delayed". Urgency is considered the hallmark symptom of overactive bladder, but it has been shown to be difficult to define or accurately describe for research or clinical purposes.[1] Urinary frequency is described as voiding eight or extra instances in a 24-hour period. Nocturia is defined as the number of times urine is passed during the period of main sleep.[2] Urinary incontinence should not be considered a disease, there is no specific cause; most individual cases are probably multifactorial. The causes of urinary incontinence are varied and in many cases not fully understood.

As noted, OAB might also now no longer defined with urgency urinary incontinence only but also additionally urgency, frequency, dysuria, and nocturia. Other phrases used detrusor overactivity, detrusor instability, detrusor hyperreflexia, and involuntary bladder contractions.[2]

Overactive bladder is a clinical diagnosis characterized by the presence of unpleasant urinary symptoms.[3] Overactive bladder (OAB) syndrome is defined by the International Association of Urological Controls as urinary urgency, with or without urgent urinary incontinence, usually frequency and/or nocturia, in the absence of

a urinary tract infection (UTI) or other obvious pathology.

An initial prognosis of OAB may be made on the idea of the history and physical examination along with laboratory tests. Anticholinergic focus on the muscarinic receptors withinside the bladder are the pharmacologic due to the fact they weaken the contractility of the detrusor muscle. However, using antimuscarinic pills is restricted in some conditions because of its complications, specifically dry mouth and constipation. Behavioral therapies that specialized in nutritional and way of life modification and pelvic ground muscle sports is likewise beneficial withinside the control of OAB and can be utilized by itself or along with antimuscarinic.

Epidemiology

The results of a survey conducted by the Department of Geriatrics, Department of Internal Medicine, National Central General Hospital, Cipto Mangunkusumo Hospital (RSCM) among 208 subject s from the elderly in Jakarta, showed the rate suffering from stress urinary incontinence (UI) disease was 32.2%. The national unemployment rate in Indonesia is estimated to be relatively high.[4]

Women are more commonly affected and the incidence increases with age; American studies show a prevalence up to 43% in women and 27% in men over the age of 40. There were significant differences between racial/ethnic groups, with overactive bladder being highest in African Americans.[5] In women, there are many possible risk factors for UI stress, such as the pelvic floor muscles damage, nerves, and connective tissue that occurs during pregnancy during labor, history of minor surgery and decreased levels of the hormone estrogen during menopause. These various factors can cause defects the internal structure of the urethral sphincter, increased mobility of the urethra, and damage to the tissues that support the urethra (anterior vaginal wall, anal levator muscle, external structures of the urethra), manifested in stress UI symptoms.[4]

Etiology

Overactive bladder is primarily a neuromuscular problem in which the detrusor muscle contracts improperly during bladder filling. These contractions usually occur regardless of the amount of urine in the bladder. Overactive bladder can have a number of different causes, both neurological and non-neurological.[2]

Sensory activity of the lower urinary tract, which is due to the sensations cause the symptomatic syndrome. The nerve endings of the lower urinary tract are concentrated under the urothelium. There, they may be exposed to urothelium-influenced mediator release and cytokines. As a result, many patients may experience urinary urgency due to impaired sensory input.[6]

Nerve damage that can cause OAB includes:[2]

1. Spinal cord injury
2. Stroke
3. Multiple sclerosis
4. Diabetic neuropathy

Detrusor overactivity can also occur in the absence of a neurological cause. Contractions can be spontaneous or caused by a rapidly filling bladder, a change in position, or even walking or coughing. Because these causes are not neurological, the urge to urinate can be suppressed for a few minutes after it is first detected.[2]

The role of M2 muscarinic receptor subtypes in the human bladder is not human bladder is not well established. Data from a small study demonstrating M2 receptor

upregulation in certain pathological conditions suggest that it may be involved in detrusor overactivity associated with obstruction and spinal cord injury.[2]

Acetylcholine binding to M3 receptor activates phospholipase C through coupling with G proteins. This action releases calcium from the sarcoplasmic reticulum and contracts the smooth muscle of the bladder. Increased sensitivity to stimulation by muscarinic receptors can lead to OAB. Leakage of acetylcholine from parasympathetic nerve endings can activate sensory afferent fibers and lead to detrusor microtremors that can lead to a sense of urgency.[2]

Sensory afferents may also play a role in the OAB. Activation of normally dormant sensory C-fibers may help induce symptoms of OAB in individuals with neuropathy and other disorders. Several types of receptors identified on sensory nerves may be involved in OAB symptoms. These include vanilloids, purines, neurokinin A, and nerve growth factor receptors. Substances such as nitric oxide, calcitonin gene-related protein, and brain-derived neurotrophic factor may also be involved in regulating sensory afferent fibers in the human bladder.[2]

The urothelium, once thought to be biologically inert, may also play a role in OAB (see figure below). The urothelium communicates directly with sub- urinary afferent nerves that act as luminal sensors. Low pH, high potassium, and elevated urine osmolality can affect sensory nerves. Suburinary afferent activation without smooth muscle alterations can lead to urinary urgency. Activation of suburinary afferent nerves by increased smooth muscle connections can cause urinary urgency and unstable detrusor contractions.[2]

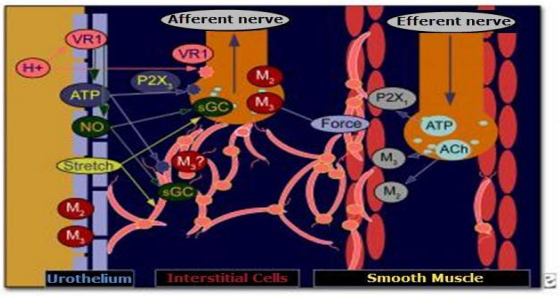

Figure1. Communication between urothelium and suburothelium. ACh—acetylcholine; ATP—adenosine triphosphate; M2—muscarinic receptor subtype 2; M3—muscarinic receptor subtype 3; NO—nitric oxide; P2X1—purinergic receptor P2X, ligand-gated ion channel 1; P2X3—purinergic receptor P2X, ligand-gated ion channel 3; sGC—soluble guanyl cyclase; VR1—vanilloid receptor 1.

Idiopathic overactive bladder is an overactive *VR1—vanilloid receptor 1*, without any neurological, metabolic, or other cause that leads to an overactive bladder or conditions that can mimic bladder overactivity, such as a urinary tract infection, bladder cancer, bladder stones, cystitis, or bladder outlet obstruction.[2]

Some medications can cause symptoms of overactive bladder. Diuretics can cause urinary incontinence by increasing bladder filling, which irritates the bladder muscles. Bethanechol can also cause urinary incontinence by stimulating smooth muscle contractions in the bladder. Heart failure or venous and peripheral vascular disease can also contribute to OAB symptoms. During the day, these people have excess fluid build up in dependent sites (feet and ankle). When they asleep, most of this fluid is mobilized and increases urine output from the kidneys, thereby increasing urine output. Many of these patients describe increased nocturia due to overactive bladder. Only in a small number of cases a specific cause cannot be determined (idiopathic VSA).[2]

Symptom

When daytime and nighttime urinary frequency and urgency symptoms (with or without urinary incontinence) are self-referencing discomfort, the patient may be diagnosed with overactive bladder.[4] In addition, a caregiver or partner may find these symptoms bothersome and direct the patient to seek care. Often, patients have endured their symptoms for a long time before seeking medical advice.[1]

History should include symptoms such as urgency, urinary incontinence, nocturia, increased frequency, dysuria, hematuria, and lower urinary tract pain. These symptoms are often best explored by symptom-based questionnaires. Clinicians should also inquire about fluid intake to assess thirst and possible irritants that may worsen lower urinary tract symptoms. Other symptoms considered may include tremor or new-onset erectile dysfunction, which may suggest a neurological condition.[7] Other existing medical conditions, such as angle-closure glaucoma, history of urinary retention, and cognitive impairment should be checked, as these are relative contraindications to antimuscarinic therapy. Similarly, hypertension may be a contraindication to treatment with beta-3 adrenergic agonists.[6]

Symptoms of an overactive bladder may only occur at night, causing a single symptom of nocturia. Differences in nocturia include nocturnal polyuria (production of more than 20-33% of total 24-hour urine output during sleep, age-dependent with 20% in young and 33% in elderly), bladder low optical. capacity, or both. In nocturnal polyuria, nocturia is usually normal or large in size in contrast to the small volume nocturia commonly seen in nocturia associated with an overactive bladder. Sleep disturbances, vascular and/or cardiac disease, and other medical conditions are commonly associated with nocturnal polyuria. OAB must also be differentiated from other conditions such as polydipsia. In OAB, urinary frequency is associated with many small gaps.[1]

As a result, the frequency and polyuria can mimic an overactive bladder; both can only be distinguished by frequency and volume histograms. In polydipsia, urinary frequency occurs with normal or large urine output, and water intake is consistent with urine output. In this case, frequency was appropriate. The frequency of hydrocephalus is a physiologically self-induced OAB and should be managed with education, taking into account fluid management. The clinical presentation of the syndrome of interstitial cystitis/bladder pain shares common symptoms of urinary frequency and urgency, with or without urinary incontinence; however, bladder and/or pelvic pain, including painful intercourse, is an important part of its presentation, whereas overactive bladder is not. Other conditions may also contribute to OAB symptoms and should be evaluated. For example, in postmenopausal patients, atrophic vaginitis may be a contributing factor to urinary incontinence symptoms. There is evidence of improvement in symptoms with the use of vaginal (but not systemic) estrogens.[1]

Physical Examination

Physical examination should include the genitourinary system, as well as digital rectal examination and assessment of prostate in men and vaginal examination in women. Urinalysis, by dipstick initially, should be performed to rule out haematuria and infection.

Although the use of urodynamics is the gold standard diagnostic test for bladder muscle overactivity, it is an invasive procedure and should therefore be limited to individuals with an overactive bladder that is resistant to heat. However, treatment should be based on the patient`s symptoms because normal urodynamics does not rule out

overactive bladder. It has been shown that overactive detrusor muscle is more common in men (69% of men with dry OAB compared with 44% of women) and those with wet OAB (90% of men versus 58% of women). The National Institute for Health and Care Excellence (NICE) advises urology prior to third-line treatment, UAE only if results may alter treatment, and American Urological Association (AUA) for those patients with complicated overactive bladder (such as those with concomitant urethral dysfunction or in those for whom the diagnosis is unclear.[5]

Management

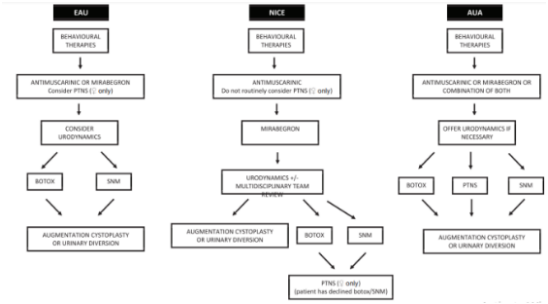

Figure 2. Comparison of NICE, EAU and AUA guidelines for the management of OAB. AUA, American Urological Association; EAU, European Association of Urology; NICE, National Institute for Health and Care Excellence; OAB, overactive bladder; PTNS, posterior tibial nerve stimulation; SNM, sacral neuromodulation.[5]

Behavioral Therapy

Behavioral therapy aim to increase voiding time interval, reduce episodes of urgency and nocturia, and prevent incontinence, by directing patients to interrupt or inhibit detrusor contractions via pelvic floor muscle training. In motivated patients, this can prove to be very efficacious reducing leakage by 50–80% and up to 30% becoming dry. Limiting fluid intake to 1–1.5L a day is recommended. Patients can significantly improve OAB symptoms by reducing fluid intake by 25%. Evidence for this remains weak however, with no significant improvement in symptoms when discontinuing caffeinated beverages. Diuretics are also known be a cause of incontinence and should be avoided where possible, particularly in the elderly.[5]

Pharmacotherapy

There are a number of antimuscarinic agents available in both transdermal and oral preparations (Table 1), and these remain the mainstay of treatment in OAB with an efficacy of 65–70% in reducing major symptoms. Side effects such as dry mouth and constipation may prove bothersome to some patients in spite of efficacy. In addition, as these agents have the ability to bind and block muscarinic receptors in the whole body, including those in the brain, there is concern regarding the anticholinergic burden in elderly patients contributing to adverse events such as falls, constipation, cognitive impairment and development of delirium. Anticholinergic scales attempt to quantify the risk versus benefits of prescribing anticholinergic medication, however there remains no consensus between the medications assessed on these scales and the degree of effect.[5]

Mirabegron is a beta-agonist that acts to facilitate bladder detrusor relaxation. Mirabegron has demonstrated sustained improvements in number of micturitions and incontinence. Intolerable side effects, such as dry mouth, are statistically less compared with antimuscarinic therapy. In addition, although there are concerns regarding blood pressure rises, this remains small and mirabegron is efficacious and safe, with no difference in treatment-emergent hypertension compared with placebo. The Medicine and Healthcare products Regulatory Agency recommends the use of mirabegron with caution in those patients with stage 2 hypertension (systolic blood pressure⩾160 mmHg and/or

diastolic⩾100mmHg). It is contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure⩾180 mmHg and/or diastolic 100mmHg).[5]

Combination therapy (antimuscarinic and beta3- agonist) may be considered in patients refractory to monotherapy. Co-administration appears to improve efficacy with minimal increase in sideeffect profile. Solifenacin and mirabegron combination therapy (in doses of 5mg and 25mg or 5mg and 50mg, respectively) is reported to have a statistically significant decrease in number of incontinence episodes and micturition compared with solifenacin or mirabegron alone. Combination therapy with 10mg solifenacin greatly increased its side-effect profile with only marginal benefit in efficacy. Although EAU guidelines recognise there may be more benefit from addition of mirabegron to solifenacin 5mg, rather than increasing solifenacin to 10mg, currently only the AUA recommends combination therapy in patients who are refractory to either, in their treatment algorithms.[5]

Virabegron is a novel selective beta-agonist that has demonstrated significant improvement in symptoms compared with placebo, as well as fewer adverse events compared with imidafenacin (7.6% 50 mg, 5.4% 100 mg versus 10.3%). At present, virabegron has not been approved by either the European Medicines Agency or the US Food and Drug Administration (FDA).

Other beta3-agonists, such as solabegron and ritobegron are currently undergoing randomised clinical trials.[5]

The clinical relevance of efficacy of antimuscarinic drugs relative to placebo has been widely discussed. However, recent large meta-analyses of the most widely used antimuscarinic drugs have clearly shown that these drugs provide a significant clinical benefit. None of the commonly used antimuscarinic drugs (darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine, and trospium) are an ideal first-line treatment for all OAB/detrusor overactivity (DO) patients. Optimal treatment should be individualised, considering the patient's comorbidities and concomitant medications and the pharmacologic profiles of different drugs.[8]

	Starting dose regimen*	Dose escalation*
Darifenacin	7.5mg	15mg
Fesoterodine	4mg	8mg
Imidafenacin	0.1mg bid	0.2mg bid
Oxybutynin**	10mg ER or 5mg IR bid or tid	115-20mg ER or 5mg qid
Propiverine**	30mg ER or 15mg IR bid	45mg ER or 15mg IR tid
Solifenacin	5mg	10mg
Tolterodine	4mg ER or 2mg IR bid	Not evaluated
Trospium	60mg ER or 20mg bid	Not evaluated

*Recommended initial dose for adults with no liver or renal function impairment; Unless noted, regimens are once-daily dosing; bid: twice a day; tid: three times a day; IR: immediate release; ER: extended release;

**Agents with mixed mechanism of action but predominant antimuscarinic action.

Table 1. Drug Choice For Management OAB

The effectiveness of botulinum toxin A has been demonstrated in a number of randomised placebo-controlled trials, with a 60% statistically significant improvement in symptoms for median duration 373days. Currently 100units onabotulinum toxin A (onabotA; BOTOX®) dissolved in 10ml of saline and injected into 20points of the bladder wall above the trigone is the only licensed formulation in Europe to treat OAB, and as third-line therapy in those who have failed behavioural therapy and pharmacotherapy in the USA. The requirement for repeat injections every 6–9 months, risk of UTIs, as well as increased post-void residuals requiring clean intermittent catheterization (CIC), may lead to patient discontinuation, thus appropriate patient selection (i.e. those willing to engage in post-void residual evaluation and CIC) is imperative. Other formulations of botulinum toxin, such as Dysport and Xeomin, although used to treat refractory OAB, are not licensed for that use. For neurogenic detrusor overactivity, BOTOX is licensed at 200 units

dissolved in 30ml of saline and given in 30 injections.[5]

Drug		Dose	Uroselective?*	Number needed to treat to achieve cure of urinary incontinence[22]	Relative risk of discontinuation (95% CI)[22]	Adverse events[12,23]
Oxybutynin	Oral	5–15 mg/day	No	9 (6–16)	1.7 (1.1–2.5)	Dry mouth (68%) Constipation (10%)
	Transdermal	3.9 mg twice weekly				Dry mouth (7%) Constipation (2.1%) Erythaema at site (8%)
Solifenacin		5–10 mg/day	Yes	9 (6–17)	1.3 (1.1–1.7)	Dry mouth (26%) Constipation (12%) Blurred vision (5%)
Darifenacin		7.5–15 mg/day	Yes		1.2 (0.8–1.8)	Dry mouth (35%) Constipation (21%)
Tolterodine		2 mg twice daily	No	12 (8–25)	1.0 (0.6–1.7)	Dry mouth (23%) Constipation (6%) Dry eyes (4%)
Trospium		20 mg twice daily	No	9 (7–12)	1.5 (1.1–1.9)	Dry mouth (22.8%) Constipation (9.5%) Abdominal pain (3.1%)
Fesoterodine		4–8 mg once daily	No	8 (5–17)	2.0 (1.3–3.1)	Dry mouth (87%) Constipation (87%)
Mirabegron		25–50 mg/day	NA		1.22 (0.84–1.76)[24,5]	Hypertension (6.9%)

*Antimuscarinic more selective for bladder muscarinic receptor M3.
†Odds ratio.
CI, confidence interval; NA, not available; OAB, overactive bladder.

Table 2. Comparison of medications available for the management of OAB

Sacral Neuromodulation

Sacral neuromodulation (SNM) requires a twostage approach in which a percutaneous electrode is placed under fluoroscopic guidance into the sacral foramen to stimulate the S3 or S4 nerve roots. Subsequently patients undergo a test phase, and a permanent device is implanted if there is >50% improvement in symptoms. Therapeutic success rates are reported at 69.3% over a 23-year follow up, with no life threatening or irreversible adverse events (implant site pain and undesirable change in stimulation being the most reported). Lower success rates are seen in men. SNM and botulinum toxin A are comparable in terms of efficacy and safety, with no difference in reduction of UI episodes over 24 months.[5]

Posterior Tibial Nerve Stimulation

Posterior tibial nerve stimulation (PTNS) delivers electrical stimulation to the sacral micturition centres via a fine needle placed just above the medial aspect of the ankle. Treatment consists of 12 consecutive outpatient sessions, lasting 30min, usually once a week but can be up to three times a week. Effects may be sustained with maintenance therapy every 2–3 weeks, for up to 3 years. PTNS has shown a 71–79.5% patient reported response to treatment; however, there is no statistically significant benefit to PTNS compared with tolterodine. Newer implantable PTNS devices, allowing continuous tibial nerve stimulation, appear to be well tolerated, with preliminary results showing a significant improvement in UI and a similar efficacy to SNM. However, only short-term (6months) data are currently available.[5]

Augmentation Cystoplasty

Augmentation cystoplasty remains a 'last resort' option for those patients with OAB refractory to both medication and minimally invasive treatment options. Advancements in surgical technique have seen laparoscopic and robotic augmentation cystoplasty being performed with minimal morbidity. Patients should be counselled for the need to perform CIC post procedure; however, it must be noted urinary retention and the need for CIC is preferable for some patients when compared with severe intractable frequency, urgency and urgency incontinence. In those unable or unwilling to perform CIC, urinary diversion, in the form of an ileal conduit/ stoma, may be an option. Outcomes remain excellent with a continence rate of 93% in those with OAB (compared with 78% in neuropathic bladders). Long-term complications of augmentation, including recurrent UTIs, bladder stone and possible malignancy are well documented. Long-term surveillance cystoscopy is controversial. It has been suggested that in asymptomatic patients, annual surveillance cystoscopy is not required, with no evidence of malignancy in at least the first 10 years after augmentation cystoplasty.[5]

Conclusion

Overactive bladder (OAB) diagnosis characterized by the presence of unpleasant urinary symptoms. Women are more commonly affected and the incidence increases with age. OAB currently has many treatment options. The importance of patient education about treatment options, including lack of treatment is critical, as it is important for both clinician and patient to perceive her OAB as an incurable syndrome rather than a disease. Given the choice, most patients appear to option for minimally invasive surgery (ie, OnabotA or SNM) with preoperative preparation associated with improved patient outcomes.

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