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Approach to female urinary incontinence: Part 1: Medical Management

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Introduction
Urinary incontinence is defined as the involuntary loss of urine.[1] It is a ubiquitous disorder, thought to occur more commonly than more familiar health issues such as hypertension, diabetes, and depression. It is a condition whose profile of affected patients includes women of all age groups and which transcends socio-economic and cultural circumstance.[2] Given the above, the social, emotional, and economic impact of the disease on individuals and communities is self-evident.

The true prevalence of urinary incontinence world-wide, and in South Africa is essentially unknown. Community based studies have reported the prevalence as ranging between 14% and 67%, showing a large discrepancy from the estimates of physician-based studies, which show an estimated prevalence of between 0.5-5%.[2,3,4] This disparity is thought to arise from a combination of under-reporting, under-diagnosis, and under-treatment of the disease.

Types of urinary incontinence
For clinical purposes, incontinence can be divided into three sub-types as defined by the International Urogynaelogical Association / International Continence Society (IUGA/ICS) joint report.[5]

SUI makes up approximately half of all reported urinary incontinence, with the next prevalent subtype being MUI making up around a third, and UUI accounting for just over 10% of all urinary incontinence.[6]

Table 1. Types of UI as characterised by the IUGA/ICS joint report on the terminology for female pelvic floor dysfunction.[1]

Type	Definition
Stress urinary incontinence (SUI)	'involuntary loss of urine' on effort or physical exertion, or from sneezing or coughing
Urge urinary incontinence (UUI)	The state of involuntary loss of urine that is associated with urgency
Mixed Urinary incontinence (MUI)	Loss of urine associated with both urgency and on physical effort as described above. MUI can be either urge, or stress predominant.

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Pathophysiology

SUI:
To maintain continence under stress (i.e. during periods of raised abdominal pressure, the urethra and bladder neck must maintain satisfactory intra-urethral pressures at rest. Inadequate intra-urethral pressures will allow for incomplete transmission of abdominal pressure to the urethra, and therefore compromised continence.[2]

Proximal urethra hypermobility (as result of disruption of the musculofascial architecture) and descent have also been postulated as contributing to SUI.

Nerve dysfunction, particularly secondary to pudendal nerve damage during childbirth may also contribute to SUI by causing atrophy of portions of the levator ani and/or other voluntary muscles forming the pelvic floor and perineum.[2] Gyhagen et al. showed that 20 years later, vaginal delivery correlated with a 67% increased risk of SUI. They found that when compared to caesarean section, the risk of UI following vaginal delivery after 10 years was 275%, illustrating that to prevent one case of UI it is necessary to perform 9 caesarean sections.[6]

Other factors which may contribute to the development or severity of SUI include disease which cause chronically raised abdominal pressures such as obesity, chronic cough of diverse aetiology, and pelvic tumours.[2,6]

UUI:
The pathophysiology of UUI, otherwise known as Overactive Bladder (wet) is complex and multifactorial. It is thought that the symptoms of UUI can be brought about by dysfunction in smooth muscle contractility and/or changes in bladder innervation. Specific conditions such as outlet obstruction, inflammation, and spinal cord injury, and even some mood disorders (such as depression, anxiety, and attention deficit disorder) have all been linked to UUI.[7]

Assessment and investigations
According to the American College of Obstetricians and Gynaecologists, there are six aspects of clinical evaluation to be covered for all patients with UI. Although typically described for the evaluation of uncomplicated stress incontinence, the principles outlined apply to all patients who present with the complaint of involuntary loss of urine.[8]

These are:
1. History
2. Urinalysis

3. Physical examination
4. Clinical demonstration of SUI
5. Urethral mobility assessment
6. Postvoid residual volume assessment

History:
Important aspects of the history include elucidating the type and nature of the incontinence, the frequency and severity of the disease, as well as its impact on daily living. Validated questionnaires are available to assist the clinician in the assessment of disease severity and determine the proportionate contributions

Table 2. Validated Questionnaires to evaluate the impact of urinary incontinence as suggested by the ACOG.[8]

UDI	Urogenital Distress Inventory
IIQ	Incontinence Impact Questionnaire
QUID	Questionnaire for Urinary Incontinence Diagnosis
ISI	Incontinence Severity Index
ICIQ	International Consultation in Incontinence Questionnaire

of urge and stress symptoms to the overall clinical picture (see table 2). Short form questionnaires are quick, simple and relatively easy to complete, and their value in the characterisation of incontinence in the clinical setting should not be underestimated.[8]

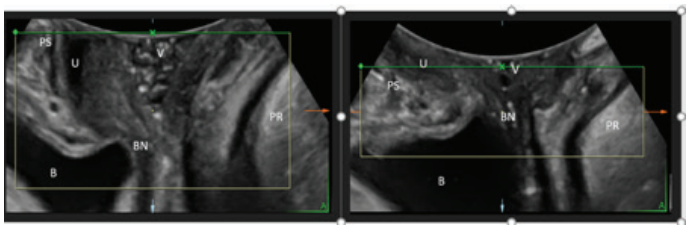
Urinalysis:
The main purpose of urinalysis is to exclude underlying infections, which can mimic and/or exacerbate incontinence symptoms, and should be treated prior to further investigations or management.[8]

Physical examination:
The aim of the physical examination is to eliminate any factors which may potentially confound or aggravate the assessment or management of the incontinence, such as vaginal discharge, urethral diverticulae, and extra-urethral causes of incontinence such as vaginal fistulae or ectopic ureters. Pelvic organ prolapse is also known to complicate the assessment of incontinence, and in these cases an effort should be made to reduce the prolapse to unmask potential stress incontinence during the physical examination.[8]

Clinical demonstration of SUI:
It is important to clinically demonstrate leakage of urine prior to incontinence procedures. The patient should have a comfortably full bladder (approximately 300ml), and if no leakage is demonstrated on cough in the supine position, the test should be repeated with the patient standing before the test can be deemed negative. Leakage of fluid from the urethra coinciding with cough or Valsalva is pathognomonic of SUI. Delayed urine leakage may be suggestive of cough induced detrusor overactivity. In the case of delayed emptying, or in cases where SUI cannot be demonstrated despite clear symptomatology described by the patient, urodynamic studies may be appropriate.[8]

Urethral mobility assessment:
Tests of urethral mobility include the visualisation of movement of an ear bud placed in the urethra, palpation, and the use of ultrasound. When the urethra is displaced more than thirty degrees from the horizontal plane (with the patient straining in the supine or lithotomy position) and decent of the bladder neck equal to or over 25 mm, it is regarded as hypermobile (see fig 1). Recently, the ear bud test has been replaced by trans-perineal ultrasound (TPUS) as the standard method of urethral mobility assessment, due to increased patient discomfort with the former. Urethral mobility

Figure 1. Transperineal pelvic floor ultrasound illustrating hypermobility of the urethra with significant decent of the bladder neck (BN). PS, pubic symphysis; U, urethra; V, vagina; B, bladder; BN, bladder neck; PR, puborectalis.



is indicative of SUI, and its presence is a marker for successful anti-incontinence surgery. In the absence of urethral mobility, it may behove physicians to consider alternatives to traditional anti-incontinence surgery such as urethral bulking agents.[8]

Post void residual volumes:
Post void residual (PVR) volumes are an important measure of voiding function, and only when volumes are less than 150ml should a patient be considered as having uncomplicated SUI. Large post-void residual volumes should alert the physician to the possibility of a dysfunction in the mechanism of bladder emptying, or to chronic urinary retention, and should prompt further evaluation of the above.[8]

Further investigations are directed by your findings and have been detailed in the table below.

Table 3. Special investigations in the assessment of urinary incontinence.[8]

SIMPLE INVESTIGATIONS	
	Screening for diabetes
	Screening for urinary tract infections
	Measurement of PVR
	Bladder diary
SPECIAL INVESTIGATIONS	
	Urodynamic Studies (UDS) with/without EMG
	Urethral pressure profilometry (UPP)
	TPUS

Treatment options

Conservative management:
General measures such as limiting overall fluid intake, decreasing intake of caffeine, alcohol, and carbonated drinks are standard practice in the initial management of UI. Other strategies such as weight loss and smoking cessation are also recommended.[9]

SUI : Pelvic floor muscle therapy forms the foundation of conservative management for SUI. Although limited by small study

sizes and a number of confounding factors a 2011 meta-analysis of the available research of 21 studies including 1490 women demonstrated that women who undertook regular and continual PFMT with a practitioner directing their exercise and supervising their progress showed superior subjective improvement.[10] This in conjunction with manual or biofeedback strategies can improve exercise technique and outcomes. Devices, including catheters, incontinence tampons, incontinence pessaries are available for those patients who are unfit for, or do not desire surgery including pregnant women, and those in whom previous surgical interventions have failed. Benefits of such conservative therapy includes a low risk profile and cost, and they achieve rapid results.

UUI: In the absence of cognitive impairment, lifestyle modification is the first line in the management of UUI. This includes but is not limited to bladder drill/retraining, pelvic floor muscle therapy (PFMT) including the use of biofeedback strategies. Patients with some element of cognitive impairment present more of a challenge in this regard, but some improvement has been reported with methods such as scheduled voiding, prompted voiding and habit training.

MUI: The aim of treatment for MUI is to elicit the predominant complaint and triage management accordingly.[11]

Pharmacologic management:
SUI:
Alpha-agonists:
Currently there are no effective medications for the treatment of SUI. Theoretically, alpha-agonists (pseudoephedrine) should result in urethral compression and thereby aid in the treatment of SUI, but clinical trials have yet to prove any real efficacy in this regard.[9]

Duloxetine:
The use of the anti-depressant Duloxetine for SUI has been approved by the FDA and the European Medicines Agency. . Its use has been hampered by its side-effect profile, which includes aggravating mental health issues and increased suicidal ideation . In 2005 the Cochrane Database published an analysis of the use of SNRI's such as Duloxetine in the treatment of SUI. The results of that study showed a miniscule improvement of quality of life and incontinence episodes in patients with stress predominant SUI. The authors of found that the most common side effect of the medication is nausea, a side effect which led to a 16% discontinuation rate on its own. Given the questionable applicability to clinical practice, as well as the fact that the long term effects of the drug were yet to be established, the authors concluded that further good quality trials on the topic are needed before consensus on the topic could be reached.[12,13] As of last publication, the UK National Institute for Health and Care Excellence (NICE) guideline states that practitioners should not consider the use of Duloxetine as first line treatment in women with stress predominant SUI. It goes on to state that while it does not generally consider Duloxetine to be a viable second-line treatment, it may be offered to patients who show a preference for medical management or who are not surgical candidates for whatever reason.[14]

Oestrogen:
The use of Oestrogen for the treatment of SUI is contentious. Multiple studies have been undertaken to elucidate the relationship between SUI and circulating endogenous sex hormones, with conflicting results. This conflict can partially be explained by the fact that many of the available studies have looked at the effect of oestrogen and urinary incontinence (as an umbrella term), or focused specifically on UUI, and the role of oestrogen and SUI has not been fully explored.[15,16] Compounding the conflict is the fact that the effect of the hormone appears to differ according to the route of administration. A Cochrane review in 2012 demonstrated that local oestrogen creams had a small favourable effect on urinary incontinence. In contrast to this, oral oestrogens appeared to worsen urinary tract symptoms. The authors of the 2012 review concluded that additional large robust trials were needed before a thorough recommendation could be provided.[17] The European Association of Urology and NICE Guidelines currently endorse the use of topical vaginal creams in postmenopausal women with UI in the presence of vaginal atrophy.[18,19] Recently, a prospective multinational pilot study looking at the effect of topical vaginal oestrogen creams on vaginal atrophy and SUI symptoms was undertaken, with South Africa as one of the participating centres. The authors found that subjective SUI symptoms in postmenopausal women were lessened by topical oestrogen creams. Although further long term follow-up is needed, in view of the fact that oestrogen cream is safe, relatively inexpensive, and readily available- it may be of use in patients requesting conservative management, of for those awaiting definitive surgical treatment.[16]

Desmopressin:
There is some evidence that the use of Desmopressin, a synthetic vasopressin, may decrease urinary incontinence episodes within

Table 4. Main anticholinergics available in South Africa.[21]

Antimuscarinics	Drug name	Brand name South Africa	Dosage guidance	Special features
	Tolterodine Tartrate	Detrusitol XL	4mg daily	
	Trospium Chloride	Uricon	20mg twice daily	Quaternary amine. Theroretically less CNS effects as does not cross blood brain barrier
	Solifenacin Succinate	Vesicare	5mg - 10 mg daily	
	Darifenacin Hydrobromide	Enablex	7.5mg – 15mg three times daily	Tertiary amine derivative. Selective M3 receptor antagonist
Mixed Action	Oxybutynin Hydrochloride	Ditropan	2.5mg twice daily - 5mg three times a day	
	Oxybutynin Hydrochloride ER	Lyrinel XL	5mg daily – 20mg daily	
	Propiverine hydrochloride	Detrunorm	15mg daily to three times daily	Tertiary amine with antimuscarininc and musculotrophic effects. Also available as ER (Detrunorm XL, dose 30mg daily). Long term clinical data limited.

four hours, but that no long-term improvement is shown with chronic use.[20] Based on the current evidence, the EAU therefore recommends that Desmopressin should not be used as a long-term measure for the control of incontinence, but may be used on occasion as interim measure. Patients treated in this fashion must be warned that the drug is not currently approved by the FDA for the purpose. The NICE guidelines state that Desmopressin should be offered only to that subset of patients that suffer from nocturia in addition to daytime UI, and caution against its use in patients with cystic fibrosis, and those over 65 years of age with pre-existing cardiovascular dysfunction.[18]

UUI

Anticholinergics:

Although they vary somewhat in structure and functional profile, all anticholinergics affect the detrusor muscle and its afferent innervation. Anticholinergics are widely used in the treatment of UUI, the merits being that they are relatively safe, can be quite inexpensive, and have shown significant efficacy over placebo. The major disadvantage of anticholinergic medications is the side effect profile, particularly the effect on cognitive function. Given that the prevalence of urinary incontinence increases with age, which is in itself a risk factor for altered cognitive states, the addition of anticholinergics may increase the probability of mental health decline. In an attempt to circumvent the adverse side effects, various iterations of anticholinergics are available on the market today.[21] Head to head comparison data is lacking, but in 2012 a systematic review by the Cochrane Library found that the continuation rate for Tolterodine when compared to Oxybutynin was higher due to an improved side effect profile. In terms of quality of life, cure or improvement, and adverse effects, Solifenacin was found to perform better than Tolterodine. Fesoterodine was also found to perform better than Tolterodine in the above categories, but had a higher drug withdrawal rate due to adverse effects. Extended release (ER) formulations (of Oxybutinin and Tolerodene had equivalent efficacy, but with mild improvement of dry mouth at up to three month that was more marked in the ER Tolterodene group.[22]

Mirabegron:

Stimulation of the sympathetic nervous system via β3-receptor agonists causes relaxation of the detrusor muscle, facilitating storage of urine by the bladder. Mirebegron is a selective β3-agonist which has been the focus of large, phase III randomised controlled trials, which concluded that use of Mirebegron effected a reduction in incontinence episodes, and an improvement of quality of life when compared to placebo.[23,24] A 2014 mixed treatment comparison analysis of 44 studies found that compared to most of the drugs currently approved for UUI in Europe, Mirebegron showed a effectiveness against UUI. The only exception to this was Solifenacin at a dose of 10mg which proved superior in improving frequency of UUI episodes when compared to 50mg Mirebegron. It should be noted, however that patients administered Solifenacin at that dose, or Fesoteradine 8mg reported the highest incidence detrimental effects, specifically dry mouth. In contrast, the incidence of dry mouth associated with Mirebegron was equitable with placebo.[25] Given the reduction in antimuscarinic side effects, Mirebegron may prove to be a viable option for those patients who require an alternative to anticholinergics, whether due to adverse effects or non responders. Combinations of newer generation anticholinergics and Miregbegron have also been investigated, with the aim of minimising adverse effects while obtaining maximal drug efficacy. The combinations of Solifenacin and Mirebegron for the treatment of UUI has shown significant gains in terms of frequency and urgency , without the adverse affects associated with higher dose anticholinergic monotherapy.[26] The most common adverse events associated with Mirabegron include hypertension, nasopharyngitis, headache, and urinary tract infections.[25] Due to its effect on the blood pressure, it should be used with caution on patients with uncontrolled hypertension.[27]

Oestrogen:

The bulk of the evidence pertaining to Oestrogen therapy and incontinence has focused on the treatment of UUI. Although the exact pathophysiology of oestrogen in the treatment remains unclear, current evidence supports the use of oestrogen in postmenopausal women. The pathophysiology behind this may be merely the correcting that atrophic changes in the vagina, or may be due to an effect on the bladder itself.[28]

Conclusion:

Female urinary incontinence is a condition which, due to many factors including cultural and societal norms and taboos, is still under-reported and under-diagnosed. Global and local statistics on the subject are scanty, and even where we have been able to institute medical therapies large gaps still exist in our knowledge due to limited good quality data. As practitioners who has sustained relationships with their patient it behooves us to screen for, assess, and manage such conditions as they arise in our patient who we see as a matter of course yearly for annual review. Complicated cases should be referred to subspecialists for further assessment an opinion.

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