MediKredit® INTEGRATED HEALTHCARE SOLUTIONS (PTY) LTD

Medifile drug information bulletin

March 2006; 20(2)

DULOXETINE IN STRESS URINARY INCONTINENCE

Introduction

Stress urinary incontinence (SUI) is defined as involuntary loss of small volumes of urine due to an increase of intra-abdominal pressure that occurs during certain activities, e.g. coughing, sneezing, laughing or exercising. It is also known as outlet incompetence.[1] Urinary incontinence is more common in women (30% prevalence) than in men (<5% prevalence).[2] However one study showed an overall prevalence of 53.2% in women.[3] Stress and urge incontinence are common in post-menopausal women, but SUI accounts for most incontinence in women younger than 60 years.[1] Pure SUI occurs mainly in women aged 25-49 years.[4]

SUI is due to inadequate urinary sphincter function.[5] Bladder function control is maintained by voluntary and involuntary mechanisms. The external urethral sphincter and pelvic floor muscles are under voluntary control whereas the internal urethral sphincter and bladder detrusor muscles are under the control of the autonomic nervous system.[1] SUI occurs when there is a disproportionate rise in bladder pressure over urethral pressure, and certain activities can cause urine loss.[3]

Factors that contribute to SUI are[1,3,4]:

- Pregnancy
- Nerve and tissue injury during vaginal childbirth or vaginal surgery
- Age
- Inadequate oestrogen levels
- Obesity
- Diet: intake of bladder irritants e.g. caffeine, alcohol, acidic fruits, spicy foods
- Constipation
- Radiation
- Smoking
- Urinary tract infections
- Hysterectomy
- Certain neurologic lesions.

More than 75% of women report their SUI symptoms as bothersome and about 29% report their symptoms as moderate-to-extremely bothersome.[6] SUI can have a high negative impact on a patient's quality of life with respect to socialisation and sexual function.[4]

There are 2 approaches to the management of SUI: *non-drug therapy* and *drug therapy*. Non-drug therapy (NDT) includes surgery or pelvic floor muscle training in highly motivated individuals.[4] Drug therapy includes *off-label* use of α-adrenergic stimulants (α-agonists), tricyclic anti-depressants (TCA's), oestrogens and now, duloxetine[4] which has been registered by the EU for the treatment of SUI.[4,7,8]

Effective Non-drug Therapy

There are various NDTs available to treat SUI:

- Surgery is generally considered to be most effective[4,5] and some procedures have shown long term success rates of 80-96%.[3,5] However a systematic review of surgical inter-ventions found that "the effectiveness of surgery was weak and conditions speculative"[2] Surgical procedures include retropubic or laproscopic colposuspension, pubo-vaginal and suburethral sling placement[3,4], Periurethral injecting of collagen as a bulking agent is a minor procedure.[3] However, this requires multiple sessions to achieve cure and effectiveness diminishes over time.[5]
- Pelvic floor muscle training (PFMT / Kegel's exercises) is a very effective form of therapy and can rehabilitate pelvic floor muscles in highly motivated individuals. Clinical trials indicate an 80-85% improvement of SUI with PFMT.[1,5]
- Intravaginal support devices such as pessaries and urethral "plugs" may be used.[5]
- Diet counselling: Avoid or limit the intake of caffeine containing products, spicy foods and carbonated beverages as these can irritate the bladder. Also include adequate fluid intake as part of the diet. 1500-2400mls daily is recommended.[1]
- Behaviour modification e.g. scheduled toileting and prompted voiding.[1]
- Maintain optimum body weight.[1]

TABLE 1: Comparison of various features of selected agents used in the treatment of SUI[4]
Please note that none of the following drug classes are registered for treatment of SUI in South Africa

Drug Class	Hormone replacement therapy (HRT)	α-agonists	β_2-agonists	β-blockers	Tricyclic anti-depressants (TCA's)	5HT and NE reuptake inhi- bitors (SNRI's)
Example	Oestrogen ± progesterone E.g.Premarin®, Premelle®, Synapause® vaginal cream	Pseudo-ephedrine E.g. Actifed wet cough®, Sudafed sinus®	Clenbuterol[b]	Propranolol E.g. Inderal®, Purbloka®	Imipramine E.g. Tofranil®, Ethipramine®	Duloxetine E.g. Cymbalta®
Main approved uses	Vasomotor symptoms associated with menopause, vaginal atrophy, prevention of osteoporosis	Nasal decongestant	Asthma, SUI (In Japan)	Angina, hyper-tension, cardiac arrhythmias, migraine headache	Depressive dis-orders, nocturnal enuresis in children	Depressive dis-orders[4], diabetic peripheral neuro-pathic pain (FDA)[9], SUI (In the EU)[7, 8]
Rationale for use in SUI[a]	Increased (↑) urethral closure pressure and raised sensory threshold of the bladder by increasing urethral vascularity and thickness and sensitising α-adrenergic receptors in the bladder neck.[5]	↑ urethral closure pressure by stimulating urethral smooth muscle contraction.	↑ contractility of the urethral striated sphincter by relea-sing acetylcholine at the neuromuscular junction.	↑ urethral outlet resistance through bloc-kade of urethral α-adrenoceptors.	↑ contractility of smooth and/or striated muscles of the urethra and pelvic floor by enhancing the effects of norepinephrine.	Increases 5HT and NE levels in the sacral spinal cord resulting in ↑ contraction of the urethral sphincters during the urine storage phase of the micturition cycle.[5]
Efficacy	Subjective improvement has been shown with oestrogens, primarily in non-randomised trials.	Beneficial effects have been shown in open label and randomised trials.	Limited data suggest at least subjective improvement with clenbuterol.	Beneficial effects shown with prop-ranolol in open label trials; no controlled studies have been con-ducted.	Subjective and objective improve-ments demon-strated with imipramine in small, open label stud-ies; no controlled studies have been conducted.	Randomised clinical trials have shown a reduction in the frequency of incontinence and an improved QOL.[4,5]
Recommen-ded dose	Vaginal oestrogen ring: inserted into vagina every 3 months. Vaginal oestrogen cream: 0.5-1g applied nocte.[3]	Pseudo-ephedrine: 15-30mg three times daily.[3]	One study used a dose of 10mcg three times daily for urge incontinence.[17]	No data available.	Imipramine: 10-25mg three times daily.[18]	40mg twice daily; may be reduced to 20mg twice daily.[16]
Key adverse events or safety issues	Breast and ovarian cancer, stroke, heart disease.	↑ blood pressure, sleep disturbances, nausea, dry mouth, headache, tremor, palpitations, exacerbation of abnormal cardiac rhythms. α-agonists are not specific for the α-adrenoceptor and are therefore associated with a number of side effects.[4]	Tremors, tachycar-dia, headache. Clenbuterol has anabolic steroid properties and has not been approved by the FDA or MCC.[19]	Orthostatic hypotension, cardiac decompen-sation.	Anticholinergic adverse events (e.g. dry mouth, constipation), orthostatic hypotension, cardiac arrhythmia, weight gain, drowsiness.	Anticholinergic adverse events (e.g. dry mouth, constipation, nausea, fatigue, insomnia). ↑ risk of liver damage in predisposed patients. Class effect of suicidal ideation or behaviour on treatment or early after discontinu-ation.[11,16,20]

Table adapted from Drugs and Therapy Perspectives. Older pharmacological therapies for stress urinary incontinence are often unreliable, but duloxetine is a promising new option. June 2005; 21(6).
a. Main proposed mechanism of action in SUI; other potential actions may also be involved.
b. Drug not available in South Africa.

TABLE 2: Summary of some Clinical trials involving drug treatment for SUI

	Study	Population and No. of subjects	Results	Conclusion
ß-agonists	Studies have shown subjective improvement in 20-60% of patients.[3]			
$ß_2$-agonists	Treatment of urinary urge incontinence with clenbuterol *Koch J, Gunther KP, Steinberger H.*[17]	9 patients with pure stress incontinence. The patients were treated with clenbuterol on doses of 10mcg three times daily.	There were no changes in autonomous detrusor contraction or urodynamic pressure measurements after 2 weeks of treatment.	Not specified.
	A double blind clinical trial of a $ß_2$-agonist in stress incontinence. *Yasuda K et al*[4,19]	A randomised double blind study of 165 women with SUI.	There was some degree of improvement in 73% of patients using clenbuterol as compared to 55% on placebo.	Not specified.
	$ß_2$-adrenergic agonists and pelvic floor exercises for female stress incontinence. *Ishiko O et al*[19]	A randomised trial of 61 women with SUI.	Clenbuterol + PFMT improved SUI in 89.5% of women as compared to clenbuterol alone (76.9%) and PFMT alone (52.6%).[19]	Not specified.
ß-blockers	Some clinical trials have shown some benefit with the use of Propranolol in SUI but further well designed studies are required to determine place in the management of SUI.[4]			
Hormone replacement therapy (HRT)	Postmenopausal Hormones and Incontinence: The Heart and Estrogen/Progestin Replacement Study. *Grady D et al*[4,21]	A randomised blinded trial of 1525 postmenopausal women.	Results showed that the benefits of oestrogen were offset by progesterone. 26% of patients showed improvement on placebo as compared to 21% on oestrogen + progesterone and 39% on HRT felt a worsening of symptoms as compared to 27% on placebo.	Oestrogen + progesterone therapy was associated with a worsening of symptoms in older postmenopausal women.
	Oestrogens for urinary incontinence in women (Cochrane review) *Moehrer B et al*[22]	28 trials of 2926 women with sample size ranges between 16-1525.	• 15 trials compared oestrogen and placebo (374 women vs 344): There was a subjective impression of cure with oestrogen for all categories of incontinence (36% vs 21%; RR for cure1.61, 95% CI=1.04-2.49). • When subjective cure and improvement were considered together then there was an improvement of 43% on treatment vs 27% with placebo for SUI.	• Oestrogen can be considered as treatment to improve or cure incontinence but seems more effective in urge incontinence. • Oestrogen and progesterone together seemed to reduce probability of cure or improvement.
Tricyclic anti-depressants (TCA's)	Conservative treatment of female stress incontinence with imipramine. *Gilja I et al*[4]	An open label study of 30 women with SUI.	Patients using imipramine showed 70% subjective continence improvement and 40% increase in mean maximal urethral closure pressure.	Not specified.
	Comparison of treatment outcomes for imipramine for female genuine stress incontinence. *Dmochowski RR et al*[4]	40 women with SUI.	There was a 60% objective improvement in continence as measured by uroflometry, stress urethral pressure profile and other measures.	Not specified.
5HT and NE reuptake inhibitors (SNRI's) - Duloxetine	Duloxetine versus placebo in the treatment of European and Canadian women with SUI. *van Kerrebroek P et al*[12]	A randomised, double-blind, placebo controlled trial of 494 women between 24-83 years with predominant symptoms of SUI.	• At doses of duloxetine 40mg twice daily, there was an overall improvement in incontinence episode frequency (IEF) vs placebo (50% vs 29%; P=0.002). • For severe patients there was an improvement in IEF of 56% with duloxetine vs 27% with placebo (P<0.001). • There was also a significant increase in the Incontinence Quality of Life (I-QOL) score for patients on duloxetine as compared to placebo.	Duloxetine may be a potential treatment for SUI.
	Duloxetine vs placebo in the treatment of SUI: a four-continent randomised clinical trial. *Millard RJ et al*[13]	A double-blind, placebo controlled study of 458 women between 27-79 years with predominant SUI.	• At doses of duloxetine 40mg twice daily, there was an overall improvement in IEF vs placebo (54% vs 40%; P=0.05). • There was also an increase in the I-QOL score for patients on duloxetine as compared to placebo (10.3 vs 6.4; P=0.007).	There was an improvement in incontinence and I-QOL with duloxetine 40mg twice daily.
	Duloxetine vs placebo for the treatment of North American women with SUI. *Dmochowski RR et al*[14]	A double-blind, placebo controlled study of 683 North American women between 22-84 years.	• At doses of duloxetine 40mg twice daily, there was an overall improvement in IEF vs placebo (50% vs 27%; P<0.001). • There was also an increase in the I-QOL score for patients on duloxetine as compared to placebo (11.0 vs 6.8; P<0.001).	The results provide evidence that support the safety and efficacy of duloxetine for the treatment of SUI.
	Duloxetine vs placebo in the treatment of SUI. *Norton PA et al*[15]	A double-blind, placebo controlled study of 553 women between 18-65 years with predominant SUI.	• On duloxetine 20mg/day, there was an overall improvement in IEF vs placebo (54% vs 41%; P=0.06). • On duloxetine 40mg/day, there was an improvement of 59% vs 41%; P=0.002. • For duloxetine 80mg/day, there was an improvement of 64% vs 41%; P<0.001.	The results provide evidence that support the safety and efficacy of duloxetine for the treatment of SUI.

Drug / Pharmacological Therapy

To date, no drugs have been registered for the treatment of SUI by the Medicines Control Council (MCC).

The goal of drug therapy is to prevent or minimise urine leakage by increasing intraurethral closure forces via increasing the tone of the urethral smooth muscle or striated sphincter muscle.[4]

Older drug treatments with α-agonists or localised oestrogens have achieved less than optimal clinical results. *Table 1* shows the differential features between drugs that have been used to treat SUI and *Table 2* gives a summary of studies involving these agents.

Anticholinergic agents such as oxybutinin [Ditropan®, Lenditro®] and tolterodine [Detrusitol®] are not appropriate or effective in the treatment of SUI.[5]

Duloxetine in SUI

Duloxetine is a serotonin (5HT) and norepinephrine (NE) reuptake inhibitor.[5] It is registered in a number of countries including South Africa for use in depressive disorders under the trade name Cymbalta®. Cymbalta® is also registered for the treatment of diabetic peripheral neuropathy with the FDA.[9] In 2004 duloxetine was registered with the EU under the trade names Yentreve®/Ariclaim® for the treatment of SUI.[7,8] However in 2005, Eli Lilly's application to the FDA was withdrawn due to the FDA's concern that the side effect risks of the drug outweigh its benefit as studies have shown a higher than expected rate of attempted suicide in adult females.[10,11] Refer to *Table 1* for dosing information in the treatment of SUI and side effect concerns.

A number of randomised double-blind placebo controlled clinical trials involving more than 2100 women have been conducted investigating the effectiveness of duloxetine in the treatment of SUI. Most trials used doses of duloxetine 40mg twice daily[12,13,14]; however, one study evaluated varied doses of duloxetine with a maximum dose of 80mg daily used in the trial.[15] Please refer to *Table 2* for more detail.

Conclusion

Clinical trials indicate duloxetine to be effective in the treatment of SUI. Recently released information however does caution against the use of duloxetine in patients at risk for liver damage and warn of the class effect of suicidal ideation or behaviour on treatment or early after discontinuation.[11,16] It is currently uncertain as to whether the drug will be approved in South Africa for the treatment of SUI due to its withdrawal of submission at the FDA. There are currently no studies available comparing the safety and efficacy of duloxetine to the other drugs used to treat SUI.

References

1. University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program, May 2002. Recommendations for the management of stress and urge urinary incontinence in women. [Online] [access 2005 November]. *http://www.guideline.gov/guidelines/FTNGC-2453.pdf*
2. Bandolier "Evidence based thinking about health care", November 1998; 57-6. Stress urinary incontinence in women. [Online] [access 2005 November]. *http://www.jr2.ox.ac.uk/bandolier/band57/b57-6.html*
3. Culligan PJ, Heit M. Urinary Incontinence in Women: Evaluation and Management. American Family Physician®. December 1, 2000;62(11):1-13.
4. Drugs and Therapy Perspectives. Older pharmacological therapies for stress urinary incontinence are often unreliable, but duloxetine is a promising new option. June 2005; 21(6).
5. Weiss BD. Selecting Medications for the Treatment of Urinary Incontinence. American Family Physician®. January 15, 2005; 71(2).
6. Fultz NH, Burgio K, Diokno, Kinchen, Obenchain R, Bump RC. Burden of stress urinary incontinence for community-dwelling women. American Journal Obstetrics and Gynecology. November 2003;189(5):1275-82.
7. Pharmaceutical News. 13 September 2004. Yentreve available in Europe for treatment of stress urinary incontinence. [Online] [access 2005 November *http://www.news-medical.net/print_article.asp?id=4725*
8. Medical News Today. 13 August 2004. Yentreve®/Ariclaim® approved in Europe for the treatment of Stress Urinary Incontinence in women. [Online] [access 2005 November].*http://www.medicalnewstoday.com/printerfriendlynews.php?newsid=12021*
9. FDA News. 7 September 2004, P04-87. FDA Approves Drug for Neuropathic Pain Associated With Diabetes. [Online] [access 2005 November]. *http://www.fda.gov/bbs/topics/news/2004/NEW01113.html*
10. Scrip World Pharmaceutical News. Lilly withdraws duloxetine incontinence filing. February 2, 2005; 3025:19.
11. FDA Alert for Healthcare Professionals. Duloxetine hydrochloride (marketed as Cymbalta): Suicidality in Pediatric and Adult Patients. FDA Alert [06/05] [Online] [access 2006 January]. *http://www.fda.gov/cder/drug/infosheets/HCP/duloxetineHCP.pdf*
12. van Kerrebroeck P, Abrams P, Lange R, Slack M, Wyndaele JJ, Yalcin I, et al. Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence. BJOG. March 2004;111(3):249-57.
13. Millard RJ , Moore K, Rencken R, Yalcin I, Bump RC; Duloxetine UI Study Group. Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomized clinical trial. BJU International. February 2004;93(3):311-8.
14. Dmochowski RR, Miklos JR, Norton PA, Zinner NR, Yalcin I, Bump RC. Duloxetine Versus Placebo for the Treatment of North American Women With Stress Urinary Incontinence. Journal of Urology. October 2003;170(4):1259-1263.
15. Norton PA, Zinner NR, Yalcin I, Bump RC; Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo in the treatment of stress urinary incontinence. American Journal of Obstetrics Gynecology. July 2002;187(1):40-8.
16. Prescriber. Yentreve® (Duloxetine) Abbreviated Prescribing Information. 19 March 2005;16(6):2.
17. Koch J, Gunther KP, Steinberger H. Treatment of urinary urge incontinence with clenbuterol (author's translation - Article in German). Deutsche Medizinische Wochenschrift (1946). 16 May 1980;105(20):724-7.
18. American Medical Directors Association. 14 May 2002. Pharmacotherapy of Urinary Incontinence. [Online] [access 2005 November]. *http://www.amda.com/clinical/urinaryincontinence/appendix_1.htm*
19. Onwude J. Stress incontinence. Clinical Evidence 2005;14:1-4. [Online] [access 2005 November]. *http://www.clinicalevidence.com/ceweb/conditionpdf/0808.pdf*
20. Cymbalta®; A3.0 NL 3600 AMP. [Online] [access 2006 January]. *http://www.fda.gov/cder/foi/label/2004/21733lbl.pdf*
21. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, and Snyder T. Postmenopausal Hormones and Incontinence: The Heart and Estrogen Progestin Replacement Study. Obstetrics & Gynecology 2001;97:116-120.
22. Moehrer B, Hextall A, Jackson S. Oestrogens for urinary incontinence in women (Cochrane Review). The Cochrane Library, 2005;2. [Online] [access 2005 November]. *http://www.cochrane.org/cochrane/revabstr/AB001405.htm*

CONTROVERSY AROUND THE USE OF RECOMBINANT BOVINE SOMATOTROPIN (rbST) IN MILK PRODUCTION
(available at www.safpj.co.za)

Contributor: Sasthrika Naidoo
Editorial Advisor: Dr J Noble

MediKredit Integrated Healthcare Solutions (Pty) Ltd ("MediKredit") 132 Jan Smuts Ave, Parkwood, PO Box 692, Parklands 2121, South Africa

Tel: (011) 770-6000 Fax: (011) 770-6325
E-mail: Medifile@medikredit.co.za
Supplement to the SA Pharmaceutical Journal - March 2006

Published by Medpharm Publications (Pty) Ltd. / Tel: (012) 664 7460,
E-mail: enquiries@medpharm.co.za