LEADING ARTICLE

Drugs 2004; 64 (14): 1503-1516
0012-6667/04/0014-1503/$34.00/0

Pharmacotherapy for Stress Urinary Incontinence

Present and Future Options

Norman R. Zinner,[1] *Stephanie C. Koke*[2] and *Lars Viktrup*[2]

1 Western Clinical Research, Inc., Torrance, California, USA
2 Lilly Research Laboratories, Indianapolis, Indiana, USA

Abstract

Stress urinary incontinence (SUI) is the accidental leakage of urine associated with physical activities such as running, jumping or lifting, or with sneezing and coughing. Worldwide, SUI is a highly prevalent condition, both in young and elderly women, and is a condition fraught with social isolation, loss of self-esteem and significant financial burden. Most women with SUI assume that it is an inevitable part of aging and 'suffer in silence', relying on absorbent pads or lifestyle changes to cope with their condition.

Unfortunately, for those who do seek medical treatment, the absence of effective and well tolerated pharmacological treatments for SUI limits the clinician's choices to behavioural modification, biofeedback and surgery. Many of the nonsurgical approaches have low success rates, particularly in the elderly and more severely afflicted. Although most continence surgeries have been reported to produce very high cure rates, many women are willing to live with their condition rather than undergo such invasive options. In an attempt to help these patients, some physicians prescribe off-label agents, including tricyclic antidepressants such as imipramine, α- and β-adrenoceptor agonists, and estrogen replacement therapy. The use of these therapies has been limited by unpredictable results and adverse reactions. In addition, acetylcholine receptor antagonists are often prescribed for SUI, despite the fact that these medications have never been shown to be effective in this condition.

This lack of a reliable pharmaceutical agent led to the development of duloxetine, a balanced dual reuptake inhibitor of serotonin and norepinephrine that is also being studied for the treatment of major depressive disorder. Based on *in vivo* data in animals, duloxetine is believed to increase the strength of urethral sphincter contractions and, thereby, prevent accidental urine leakage by increasing urethral closure forces. In clinical trials in women with SUI, duloxetine has demonstrated efficacy in reducing incontinence episodes and increasing the quality of life with no serious adverse effects. Nausea was the most common adverse event; however, in most patients it was reported early in treatment, mild-to-moderate in severity and transient. A medication such as duloxetine, if approved, would go a long way towards expanding the available treatment options for patients with SUI.

1. Epidemiology and Pathology of Stress Urinary Incontinence (SUI)

Stress urinary incontinence (SUI) is the involuntary loss of urine associated with physical activities such as running, jumping or lifting, or with sneezing and coughing.[1] SUI is the most common type of urinary incontinence in women, with 82% of women presenting with the symptom of SUI in either pure (48%) or mixed (34%) forms.[2] Pure SUI occurs primarily in women between 25 and 49 years of age, with a relative decrease thereafter with increasing age. Mixed urinary incontinence (symptoms of both SUI and urge urinary incontinence [UUI]) increases with increasing age.[3] SUI is uncommon in men except after prostate surgery.[2]

SUI is caused by insufficient urethral closure forces associated with the displacement of the urethra (urethral hypermobility) and/or the inability of the urethra to coapt and form a seal (intrinsic sphincter deficiency) during sudden increases in abdominal pressure.[4] Pregnancy and pelvic trauma during vaginal delivery are established risk factors in developing persistent SUI.[5] The prevalence of SUI 5 years after first delivery is 30%.[5] Other risk factors for SUI include obesity, constipation, smoking, chronic lung disease, neurological disorders, pelvic surgery, radiation and medications.[6,7]

Urinary incontinence can have a significant impact on quality of life. Social isolation and loneliness,[8] falls and fractures,[9] increased healthcare utilisation[10] and significant costs[11] are associated with both SUI and UUI, and problems with sexual arousal and sexual satisfaction are common.[12] Over three-quarters of women with SUI report their symptoms to be bothersome, with about 29% reporting their symptoms to be moderately to extremely bothersome.[13] The total yearly costs of urinary incontinence have been estimated at approximately $US26.3 billion (1995 value), or about $US3565 per incontinent person.[14] This includes out-of-pocket expenses for personal care items (absorbent pads) and related costs (laundry), as well as expenses by the healthcare system, mainly continence surgery and outpatient consultation. Specifically, it is estimated that one-third of all menstrual pads sold in the US are used for urinary incontinence rather than menstruation.[15]

Because SUI is frequently regarded as a hidden handicap and many women do not seek help, it is largely under-reported by patients. In a recent cross-sectional mailed survey of 29 903 US households, 37% of the female respondents reported incontinence symptoms in the past 30 days; however, only 24% had consulted a physician.[16] Reasons for not seeking treatment may include embarrassment, the belief that incontinence is a normal part of aging, lack of knowledge about medical management options, or fear of surgery.[17] However, defining the prevalence and, thus, the extent of healthcare need in a population is crucial to guiding effective health and preventive services and in clinical practice.[18,19]

2. Treatments for SUI

Treatments specific to SUI have been limited largely to continence surgery and various types of behavioural interventions, including pelvic floor muscle training.[7] Pelvic floor muscle training (e.g. Kegel exercises) if performed regularly can be effective in treating SUI,[20] but only in highly motivated women who are willing to continue an intense training programme for 15–20 weeks.[21] Unfortunately, drop-out rates are high,[22,23] efficacy is limited in women with severe incontinence and only 10–25% of elderly community-dwelling women become fully continent using this treatment.[24]

Among the various types of surgeries, retropubic colposuspension and pubovaginal sling placement appear to be most effective overall.[25,26] Tension-free vaginal tape, a newer, less invasive outpatient procedure has a success rate comparable with colposuspension or pubovaginal sling placement and is associated with a more rapid return to normal activity.[27] While surgery is generally considered the most curative, immediate and permanent treatment for SUI, published success rates vary and are based largely on data derived from nonrandomised, uncontrolled studies.[28,29]

Other treatments for SUI include injectable urethral bulking agents, which are usually administered on an outpatient basis at regular intervals of 1–3

years[30] and continence pessaries, which can provide bladder neck support and improve urinary incontinence in some women.[31]

There is currently no medication approved worldwide for the treatment of women with SUI, although there is a β-adrenoceptor agonist approved in Japan and two different α-adrenoceptor agonists approved in Portugal and Finland. In the woman who is not a candidate for conservative therapies or surgical interventions, pharmacological agents are often used off-label to alleviate the symptoms.[32] The pharmacological treatment of SUI aims at increasing intraurethral closure forces by increasing tone in the urethral smooth muscle, or by affecting tone of the striated muscles in the urethra. Although some drugs may contribute to an increase in urethral closure forces, including β-adrenoceptor antagonists and imipramine, only α-adrenoceptor agonists and estrogens alone or used together have been widely used.[32] However, these agents have not shown impressive results and are fraught with significant adverse reactions.

In this article, we review the current pharmacological agents used worldwide to treat SUI with some discussion of a new pharmacological agent that has demonstrated promising efficacy and safety in treating women with SUI (table I). Articles included in this review were identified through literature searches on Medline and EMBASE, a review of the references included in the *Incontinence* textbook,[33] as well as a manual search of the available research literature.

Table I. Drugs used to treat stress urinary incontinence (SUI)

Type	Examples	Efficacy	Safety issues
Estrogen replacement therapy	Estrogens/ progestogens	Overall subjective improvements have been demonstrated, primarily in nonrandomised studies. Assessment of the objective response on quantification of urine lost revealed no significant effect	Breast cancer Ovarian cancer Stroke Heart attack The US FDA has mandated that all labels carry a warning stating the increased risks for heart disease, heart attacks, strokes and breast cancer
α-Adrenoceptor agonists	Ephedrine Phenylpropanolamine (norephedrine)[a] Pseudoephedrine Midodrine Methoxamine Norfenefrine	Stimulated urethral smooth muscle contraction. Efficacy has been demonstrated in both open-label and randomised studies Phenylpropanolamine approved for SUI in Finland; midodrine approved for SUI in Portugal	Elevated blood pressure Sleep disturbances Nausea Dry mouth Headache Tremor Palpitations Exacerbation of abnormal cardiac rhythms
β-Adrenoceptor agonists	Clenbuterol	Hypothesised to increase contractility of urethral striated sphincter Clenbuterol approved for SUI in Japan	Tremors Tachycardia Headache
β-Adrenoceptor antagonists	Propranolol	Hypothesised to increase contractility of urethral smooth muscle. No controlled studies	Orthostatic hypotension Cardiac decompensation
Tricyclic antidepressants	Imipramine	Hypothesised to increase contractility of urethral smooth muscle. Open-label studies show some success in SUI. No controlled studies	Anticholinergic symptoms Orthostatic hypotension Cardiac arrhythmia Weight gain
Serotonin and norepinephrine reuptake inhibitors	Duloxetine	In animal studies, increased bladder capacity and rhabdosphincter activity. In randomised clinical trials, significantly decreased incontinence episodes and improved quality of life	Nausea Dry mouth Insomnia Constipation Dizziness

a Withdrawn from the US market by the FDA.

3. Pharmacological Agents Prescribed Off-Label

3.1 Hormone Replacement Therapy

Hormone replacement therapy (HRT) is generally indicated for the treatment of vasomotor symptoms associated with menopause (e.g. hot flashes), vaginal atrophy and osteoporosis. HRT, mostly in the form of estrogens, is also used in some postmenopausal women to treat SUI. The female genital and urinary tract have some common embryological origins and both are sensitive to changes in steroids. Estrogen and progesterone receptors are found throughout the vagina, urethra, bladder and the pelvic floor to varying degrees. In postmenopausal women, estrogen replacement therapy is believed to increase the urethral closure pressure, raise the sensory threshold of the bladder and increase the number of epithelial cells lining the bladder and urethra.[34] Estrogens may also increase the response to α-adrenoceptor agonists by increasing the number and sensitivity of α-adrenoceptors.[35,36]

Estrogen, because of its trophic effects on the urethral epithelium, subepithelial vascular plexus and connective tissue[37] has been considered a prime candidate for SUI therapy, but results of clinical trials have been disappointing and even controversial.[38-46] Using meta-analysis, the Hormones and Urogenital Therapy Committee examined the use of estrogens in the treatment of postmenopausal women with urinary incontinence.[42] Twenty-three original English-language articles, published between 1969 and 1992, were used as data sources. Of these, six were randomised controlled clinical studies and 17 were uncontrolled clinical studies. The results showed that there was an overall subjective improvement for all individuals with incontinence, including those with genuine stress incontinence alone. However, assessment of the objective response on quantification of fluid loss revealed no significant effect.[42] More recently, Al-Badr et al.[44] examined five major databases for literature on the effectiveness of estrogens, with or without progestogens, in treating SUI. A symptomatic or clinical improvement was detected only in nonrandomised studies; randomised trials did not document a benefit of estrogen therapy, with or without progestogens, among postmenopausal women with SUI.

The situation is further complicated by the fact that a number of different dosages of estrogen have been used with different routes of administration and durations of treatment. Estrogen may be taken in an oral form or applied to the vaginal mucosa in a cream form or by long-acting vaginal inserts. Skin patches have also been developed recently as another way to take estrogen/progestogens. In an analysis of 28 trials including 2926 women with SUI or UUI using varying combinations of estrogens, dosages, durations of treatment and lengths of follow-up, Moehrer et al.[45] found little benefit of estrogens for SUI. Analysis of all trials showed that 50% of women taking estrogens and 25% of women taking placebo showed benefit in SUI, with a greater effect among women with UUI. There were no significant differences by estrogen type, dosage or route of administration, although there were too few data to address these aspects reliably.

As part of the Heart and Estrogen/Progestin Replacement Study, Grady et al.[46] followed up 1525 postmenopausal women with urinary incontinence. The women were randomised to either daily oral estrogen plus progestogen therapy or placebo. Incontinence improved in 26% of the women assigned to placebo compared with 21% assigned to hormones, while 27% of the placebo group worsened compared with 39% of the hormone group ($p = 0.001$). This difference was evident by 4 months of treatment and was observed for both SUI and UUI. Overall, daily oral estrogen plus progestogen therapy was associated with worsening urinary incontinence in postmenopausal women. The investigators suggested that the beneficial effect of unopposed estrogen is negated by the addition of progestogen to the regimen. The investigators also hypothesised that estrogen given transvaginally might be more effective than oral estrogen, although this has been demonstrated only in small, uncontrolled trials.[46]

In light of new evidence that long-term estrogen/progestogen use increases the risk of stroke, heart

attack, and breast and ovarian cancer,[42,46-48] estrogen and progestogens have become a less attractive treatment modality for SUI. In 2003, the Women's Health Initiative study concluded that the overall health risks for estrogen with progestogen, particularly in breast cancer risk, exceeded the benefits of fracture and colon cancer risk reduction.[49] In January 2003, the US FDA mandated that all labels on estrogen and estrogen/progestogen replacement therapy be revised to carry a warning stating the increased risks for heart disease, heart attacks, strokes and breast cancer. Later in 2003, the Million Women Study was published, in which 1 084 100 British women (aged 50–64 years) were recruited between 1996 and 2001. Half of these women had used HRT; in this group, there was an increased incidence and significant risk for fatal breast cancer, particularly for estrogen/progestogen combinations.[50]

3.2 α-Adrenoceptor Agonists

The indications for α-adrenoceptor agonists vary depending on the specific agent. Most over-the-counter preparations are nasal decongestants, cough suppressants or diet pills. Prescription agents may be indicated for low blood pressure or shock. α-Adrenoceptor agonists used for treating SUI off-label include the non-subtype-selective agonists: (i) ephedrine; (ii) pseudoephedrine (stereoisomer of ephedrine); (iii) phenylpropanolamine (norephedrine), which is no longer registered in the US; and (iv) norfenefrine. The subtype-selective α_1-adrenoceptor agonists are midodrine and methoxamine.

In the past, α-adrenoceptor agonists were considered as the mainstay of pharmacotherapy for SUI because they are effective at increasing bladder outlet resistance,[51] particularly in animal models.[52] Treatment with α-adrenoceptor agonists stimulates urethral smooth muscle contraction during bladder filling and voiding, continuously increasing the urethral closure pressure.[32] Ephedrine, pseudoephedrine and phenylpropanolamine directly stimulate α- and β-adrenoceptors, but can also release norepinephrine from adrenergic nerve terminals. α-Adrenoceptor agonists have been found to be effective in stress incontinence in both open-label and controlled clinical trials.[53-57] These drugs have also been used in combination with estrogens and other nonsurgical treatments, such as pelvic floor exercises and electrical stimulation.[32,58,59] However, long-term experience with phenylpropanolamine is lacking, and because of the risk of haemorrhagic stroke in women, phenylpropanolamine was withdrawn from the US market by the FDA in 2000.[60,61]

The place of α-adrenoceptor agonists in the general treatment of SUI has not been established, though midodrine is approved for SUI in Portugal and phenylpropanolamine is approved for SUI in Finland. Midodrine is mainly prescribed for orthostatic hypotension and phenylpropanolamine is used mainly as a decongestant.[32] Midodrine was studied in a randomised, double-blind, placebo-controlled multicentre evaluation in women with SUI.[62] In over 80 women studied, midodrine did not produce significant improvement in urodynamic measures. A similar α_1-adrenoceptor agonist, methoxamine, studied in a placebo-controlled crossover trial, showed no significant increases in maximum urethral pressure compared with placebo in women with genuine SUI.[63] All patients in this trial experienced systemic adverse effects, including piloerection, headache and cold extremities. The investigators suggested that the clinical usefulness of direct, peripherally acting subtype-selective α_1-adrenoceptor agonists in the medical treatment of stress incontinence may be limited by adverse effects.

In addition, α-adrenoceptor agonists lack exclusive selectivity for urethral α-adrenoceptors and may cause elevated blood pressure, sleep disturbances, nausea, dry mouth, headache, tremor, palpitations and exacerbation of abnormal cardiac rhythms.[32] Because their effect on the urethral smooth muscle is exerted continuously, α-adrenoceptor agonists have also been associated with occasional cases of urinary retention, particularly in children.[64]

Attempts have been made to develop α-adrenoceptor agonists with selectivity for the human urethral smooth muscle. Among the three high-affinity

α_1-adrenoceptor subtypes identified in molecular cloning and functional studies (α_{1A}, α_{1B}, α_{1D}), α_{1A}-adrenoceptors appear to be most prominent in the human lower urinary tract,[65] and the most likely to be responsible for the contraction of the human urethral smooth muscle.[66] However, no drug with appropriate subtype selectivity is currently available, and the role of α-adrenoceptor agonists in the treatment of stress incontinence has yet to be established.

3.3 β-Adrenoceptor Agonists

β-Adrenoceptor agonists are indicated as bronchodilators for treating asthma. One drug in this class, clenbuterol, is a β_2-adrenoceptor agonist with an additional indication for SUI in Japan.[67] It has been suggested that β_2-adrenoceptor agonists may increase the contractility of the urethral striated sphincter by releasing acetylcholine at the neuromuscular junction.[67] In addition, β_2-adrenoceptor agonists also relax the smooth muscle of the detrusor during bladder filling;[32] however, the efficacy of clenbuterol on UUI has not been investigated.

In a placebo-controlled, double-blind trial, clenbuterol produced clinically significant improvement and increase in mean maximal urethral closure pressure (MUCP) in 165 women with SUI.[68] The number of patients reporting any degree of improvement was 56 of 77 (73%) in the clenbuterol group and 48 of 88 (55%) in the placebo group. These positive effects were suggested to be a result of an action on urethral striated muscle and/or the pelvic floor muscles. Furthermore, in a limited open-label trial, clenbuterol 20mg twice daily for 1 month produced improvement in 9 of 14 (64%) patients with mild-to-moderate SUI after prostatectomy.[69]

In a 12-week randomised trial, clenbuterol was compared with pelvic floor exercises and a combination of both in 61 female patients with SUI.[67] The frequency of SUI episodes, the volume of each leakage and the patients' own impression were the basis for the assessment of efficacy. Clenbuterol alone improved incontinence in 76.9% of patients, pelvic exercises in 52.6%, and the combination of drug and physical therapy improved incontinence in 89.5% of patients. However, to date, there have been no well designed randomised clinical trials documenting the effects of clenbuterol as a potential treatment for SUI.[32]

Adverse effects of clenbuterol are tremors, tachycardia and headache. The drug has been widely used by athletes as a CNS stimulant, and has been banned by the International Olympic Committee because of its anabolic qualities.

3.4 β-Adrenoceptor Antagonists

β-Adrenoceptor antagonists are prescribed for angina, hypertension, cardiac arrhythmia and migraine headaches. The use of β-adrenoceptor antagonists in treating SUI is based on the theory that blockade of urethral β-adrenoceptors may enhance the effects of norepinephrine on urethral α-adrenoceptors and increase urethral outlet resistance. While propranolol has been reported to have beneficial effects in the treatment of SUI in open-label trials,[70,71] there are no randomised clinical controlled trials supporting such an action. Orthostatic hypotension and cardiac decompensation are potentially serious adverse reactions with this class of drugs.

3.5 Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are indicated for depressive disorders and have been reported to have beneficial effects in patients with urinary incontinence.[32] However, imipramine, which is also indicated for nocturnal enuresis in children aged 5 years and older, is the only agent in this class that is widely used. Imipramine is usually prescribed at dosages of 50–150 mg/day. Among its other pharmacological effects, imipramine weakly inhibits the reuptake of norepinephrine and serotonin in adrenergic nerve endings. In the urethra, this can be expected to enhance the contractile effects of norepinephrine on smooth muscle.[72] Theoretically, such an action may also influence the striated muscles in the urethra and pelvic floor by effects at the spinal cord level.[32] Although it is known that TCAs such as imipramine have systemic anticholinergic

effects and, therefore, may also possess an effect on the bladder smooth muscle, the mechanism of action in treating detrusor muscle overactivity and UUI has not been determined.

In an open-label study on 30 women with SUI, Gilja et al.[73] reported that imipramine 75 mg/day produced subjective continence in 21 patients and increased mean MUCP from 34 to 48mm Hg. In a prospective study, Lin et al.[74] assessed the efficacy of imipramine (25mg three times daily for 3 months) as a treatment for genuine SUI in 40 women. A 20-minute pad test, uroflowmetry, filling and voiding cystometry, and stress urethral pressure profile were performed before and after treatment. Using these objective measures, imipramine was found to improve SUI in 60% of the women studied.[74] Using quality-of-life questionnaires, Woodman et al.[75] found that treatment with imipramine was associated with clinical improvement in 72% of 22 women with UUI. Despite this limited success in treating incontinence, imipramine has not been studied in quality randomised clinical trials.[32]

TCAs are associated with several well-known adverse effects. Blockade of muscarinic cholinergic receptors causes frequent adverse effects, such as dry mouth, blurred vision, constipation, urinary retention and orthostatic hypotension.[76] Due to blockade of histamine H_1 receptors, TCAs may also cause sedation and drowsiness,[76] as well as disorientation and falls, a particularly troublesome adverse effect in elderly patients. For patients with a history of heart failure, TCAs can cause heart rhythm abnormalities and decrease the force of cardiac contractions.[76] Overdosage of TCAs can cause death; in fact, TCAs are the most commonly used drugs in suicide by poisoning.[76] Withdrawal symptoms may also occur, especially in geriatric patients.

3.6 Acetylcholine Receptor Antagonists

Acetylcholine receptor antagonists/muscarinic receptor antagonists, including tolterodine and oxybutynin, are indicated for the treatment of bladder overactivity. Acetylcholine receptor antagonists decrease the tendency of the bladder to contract inappropriately by blocking acetylcholine binding at its peripheral (muscarinic) receptor on the bladder smooth muscle.[32] An anticholinergic effect on the urethral muscles has not been documented. Pharmacotherapy of SUI with tolterodine has not proven to be any more effective than placebo.[77] There have been no controlled trials with oxybutynin in the treatment of SUI.

4. New Agents Under Study for SUI

4.1 Serotonin And Norepinephrine Reuptake Inhibitors

Recent *in vivo* animal studies have demonstrated that serotonin and norepinephrine neurotransmitters are involved in the micturition cycle. Studies in the anaesthetised cat model have shown that serotonin 5-HT receptor agonists suppress parasympathetic activity and enhance sympathetic and somatic activity in the bladder.[78-80] These actions relax the bladder and facilitate urine storage. Noradrenergic agonists and antagonists can stimulate or inhibit the sympathetic and somatic activity in the lower urinary tract, depending on the adrenoceptor subtype with which they interact.[80-82]

Venlafaxine, has been shown to increase urethral perfusion pressure in animals,[83] although, paradoxically, there have been some case reports of patients taking this drug for depression who developed incontinence.[84] Venlafaxine has not been studied for the treatment of SUI in women.

Duloxetine, a balanced serotonin and norepinephrine reuptake inhibitor,[85] is currently being investigated for the treatment of SUI in women,[86-88] as well as for the treatment of depression.[89] Duloxetine is believed to affect SUI by blocking the reuptake of serotonin and norepinephrine in the Onuf's nucleus, an area in the sacral spinal cord.[87] The Onuf's nucleus is unique in that it contains a high density of 5-HT and norepinephrine receptors, and pudendal motor neurons located in Onuf's nucleus regulate the urethral striated muscle sphincter (rhabdosphincter). Serotonin and norepinephrine stimulate these neurons, increasing the strength of urethral sphincter contractions and presumably de-

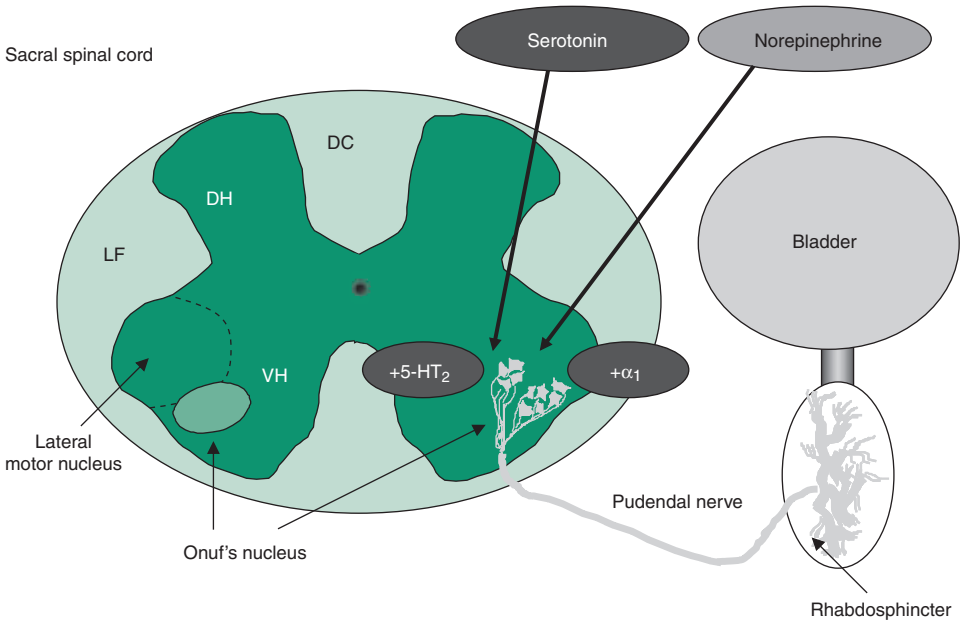

Fig. 1. Mechanism of action of serotonin and norepinephrine reuptake inhibitors. Schematic of a portion of the sacral spinal cord showing innervation from the ventral horn (VH) area (Onuf's nucleus) to the rhabdosphincter, the outer striated muscle controlling the urethral opening. The striated urethral sphincter is innervated by the pudendal nerve, which contains the axons of motor neurons whose cell bodies are located in Onuf's nucleus. **+α_1** = α_1-adrenoceptors; **+5-HT$_2$** = serotonin 5-HT$_2$ receptors; **DC** = dorsal commissure; **DH** = dorsal horn; **LF** = lateral funiculus.

creasing accidental urine leakage by increasing urethral closure forces (figure 1).

In the rat, Wong et al.[90] demonstrated that duloxetine effectively blocked the reuptake of both neurotransmitters, but showed little or no inhibition of dopamine reuptake or affinity for histaminergic, dopaminergic, adrenergic or cholinergic receptors. Although the TCAs appear to produce adverse effects by antagonising the central as well as the peripheral muscarinic, histaminergic and adrenoceptors, duloxetine, with its relatively weak affinity for these neuronal receptors, appears to have a lower propensity for adverse effects. On the other hand, duloxetine does produce other pharmacological responses consistent with its action as an inhibitor of serotonin and norepinephrine reuptake, including antidepressant properties.[90]

In an acetic acid-induced model of irritated bladder in the cat, duloxetine significantly increased bladder capacity and muscle activity of the urethral sphincter.[91] In this study, bladder contractions evoked by direct electrical stimulation of efferent fibres in the pelvic nerve were not affected by duloxetine, suggesting these effects were centrally mediated via both motor efferent and sensory afferent modulation. The effect of duloxetine on improving bladder storage appears to be unique to the dual serotonin and norepinephrine reuptake inhibition in a single molecule and is not duplicated by the coadministration of two separate single reuptake inhibitors.[92] *In vitro* and *in vivo* studies show that duloxetine inhibits serotonin and norepinephrine reuptake more potently than venlafaxine, and that larger doses of venlafaxine were required to achieve similar effects.[85,92]

Phase I safety studies have shown that duloxetine is well tolerated in healthy volunteers.[93-97] In a large phase II trial conducted at 48 study centres in the US, duloxetine efficacy and safety was evaluated in women diagnosed with a predominant symptom of SUI.[86] Investigators studied 533 women aged 18–65 years with at least four incontinent

episodes per week, normal bladder capacity and no prior continence surgery. Of the 553 women enrolled in this trial, 86 also underwent urodynamic testing; 92% were found to have urodynamic SUI. Women were randomised to 12 weeks of treatment with placebo (n = 138) or duloxetine at one of three doses (20 [n = 138], 40 [n = 137] or 80 mg/day [n = 140]).

As shown in table II, duloxetine was associated with significant dose-dependent decreases in incontinence episode frequency (IEF) that paralleled improvements in the Patient Global Impression of Improvement (PGI-I) scale and the Incontinence Quality of Life (I-QOL) questionnaire. Based on an analysis of pooled diary data, the median IEF decrease with placebo was 41% compared with 54% for duloxetine 20 mg/day ($p = 0.06$), 59% for duloxetine 40 mg/day ($p = 0.002$) and 64% for duloxetine 80 mg/day ($p < 0.001$). Half of the patients taking duloxetine 80 mg/day had at least a 64% reduction in IEF ($p < 0.001$ vs placebo), whereas 67% had at least a 50% reduction in IEF ($p = 0.001$ vs placebo). The percentage of patients experiencing a complete elimination of their incontinence (zero incontinent episodes at endpoint) was 16.4% for duloxetine 20 mg/day, 24.4% for duloxetine 40 mg/day, 18.7% for duloxetine 80 mg/day and 15.2% for placebo (no significant differences between treatment groups).[86]

The improvements in IEF were significant at the first treatment visit (4 weeks after treatment began) despite significant concurrent dose-dependent increases in average voiding interval in the duloxetine groups compared with the placebo group. Similar statistically significant improvements were demonstrated in a subgroup of 163 patients who had more severe SUI (at least 14 incontinent episodes per week). Specifically, in this patient subset, duloxetine resulted in a 49–64% reduction in IEF compared with 30% in the placebo group. Duloxetine was well tolerated and no adverse event was considered clinically severe. Discontinuation rates for adverse events were 5% for placebo and 9%, 12% and 15% for duloxetine 20, 40 and 80 mg/day, respectively ($p = 0.04$). Nausea was the most common symptom that led to discontinuation. On the basis of this data, duloxetine 80 mg/day (40mg twice daily) was determined to be the optimum dose in women with SUI.[86]

Similar results were seen in a recent placebo-controlled, phase III clinical study in 683 North American women aged 22–84 years with a weekly IEF of at least seven episodes (table III).[87] Women were randomly assigned to receive placebo or duloxetine 80 mg/day (40mg twice daily) for 12 weeks. Duloxetine was associated with a significant decrease in IEF (median decrease of 50% vs 27%, $p < 0.001$) and improvements in the I-QOL scores (+11 vs +6.8, $p < 0.001$). These improvements were associated with significant increases in voiding intervals compared with placebo (20 vs 2 minutes, $p < 0.001$). At endpoint, 10.5% of duloxetine-treated patients and 5.9% of placebo-treated patients had no incontinent episodes ($p < 0.05$). In a subgroup of 436 patients with more severe SUI (≥14 incontinent episodes per week), there were similar significant

Table II. Phase II double-blind, placebo-controlled clinical experience with duloxetine in patients with stress urinary incontinence[86]

Treatment group	All women (n = 553)		More severe strata (≥14 incontinent episodes per week, n = 163)	
	median IEF decrease	mean I-QOL improvement	median IEF decrease	mean I-QOL improvement
Duloxetine 20 mg/day (n = 138)	−54%	+5.3	−49%	+3.1
Duloxetine 40 mg/day (n = 137)	−59%[a]	+7.8	−63%[a]	+9.4
Duloxetine 80 mg/day (n = 140)	−64%[a]	+9.3[a]	−64%[a]	+13.3[a]
Placebo (n = 138)	−41%	+5.8	−30%	+4.1

a $p < 0.05$ vs placebo (ANOVA with treatment and site as effects).

IEF = incontinence episode frequency; **I-QOL** = Incontinence Quality of Life questionnaire.

Table III. Phase III double-blind, placebo-controlled clinical experience with duloxetine in patients with stress urinary incontinence[87]

Treatment group	All women (n = 683)		More severe strata (≥14 incontinent episodes per week, n = 436)	
	median IEF decrease	mean I-QOL improvement	median IEF decrease	mean I-QOL improvement
Duloxetine 80 mg/day (40mg twice daily) [n = 344]	−50%	+11.0	−52%	+12.8
Placebo (n = 339)	−27%	+6.8	−25%	+7.4
p-Value	<0.001	<0.001	<0.001	<0.001

IEF = incontinence episode frequency; **I-QOL** = Incontinence Quality of Life questionnaire.

improvements in both IEF and I-QOL. The PGI-I results demonstrated that 62% of duloxetine-treated patients considered their bladder condition to be better on treatment compared with 39.6% of placebo-treated patients ($p < 0.001$). In addition, duloxetine subjects demonstrated statistically significant improvements compared with placebo in the three I-QOL domains of avoidance and limiting behaviour, social embarrassment and psychosocial impact.[87]

A concurrent phase III, placebo-controlled trial in 494 women with SUI was conducted in several clinical centres in Europe and Canada.[88] Compared with placebo, duloxetine treatment resulted in a significant decrease in IEF (median decrease of 50% vs 29%, $p = 0.002$) with comparable significant improvements in the more severely incontinent patient subgroup. A total of 52% of women taking duloxetine showed a 50–100% reduction in IEF compared with 34% of women taking placebo ($p < 0.001$). For those patients who completed the 12-week protocol, the duloxetine group had significantly better improvements in I-QOL scores than the placebo group (7.3 vs 4.3, $p = 0.008$).[88]

A recent meta-analysis of four studies conducted in 1913 women at 186 study centres in Africa, Australia, Europe, North America and South America provided additional evidence for the efficacy of duloxetine.[98] Compared with placebo duloxetine was associated with a significant decrease in IEF (median decrease of 52% vs 33%, $p < 0.001$) and improvements in the I-QOL scores (+9.2 vs +5.9, $p < 0.001$). The favourable treatment response with duloxetine was apparent within 4 weeks and was maintained for 3 months in the double-blind trials and for 1 year in the open-label trials.[98]

The placebo response observed in these studies was sizeable, with reductions in IEF varying between 27% and 41%. However, high placebo response rates are not unusual in SUI clinical trials. Dubeau and Khullar[99] reported a 75% reduction in SUI episodes in the placebo-treated group from a placebo-controlled muscarinic receptor antagonist drug trial in women with mixed stress and urge incontinence. This SUI placebo response is not limited to pharmaceutical trials, as Ramsay and Thou[100] reported a response in 64% placebo response for women with SUI treated with sham pelvic floor muscle training. Some of this improvement is related to active participation in the trial and exposure to the research setting: the Hawthorne effect.[101] In these studies, duloxetine was well tolerated, with nausea being the most common adverse event. In the North American phase III trial,[87] discontinuation rates for adverse events were 8% for placebo and 22% for duloxetine ($p < 0.001$), with nausea being the most common reason for discontinuation (5.7%). Nausea tended to be mild-to-moderate, transient (lasting 1 week to 1 month) and not progressive; 57 of 69 (83%) women who experienced nausea while taking duloxetine completed the trial.[87] Nearly identical results were seen in the phase III trial conducted in Europe and Canada.[88] Although cardiovascular data are not yet available in women with SUI, pooled data from six double-blind, placebo-controlled studies in patients with depression (n = 1755) showed that duloxetine was not associated with sustained elevations of blood pressure and did not prolong corrected QT intervals. Duloxetine significantly increased heart rate by approximately 2 beats per minute compared with placebo.[102]

Whereas short-term data from these clinical trials have shown that duloxetine is not associated with significant adverse reactions, long-term safety data are not yet available in women with SUI. However, preliminary data from a long-term study in patients with depression indicate that after 1 year of use, duloxetine was not associated with changes in blood pressure, heart rate or ECG intervals.[103] Another long-term study in patients with depression revealed that, among patients with baseline sexual dysfunction, sexual function improved (Arizona Sexual Experience Scale total score reduced) in 70.9% of duloxetine-treated patients compared with 61% of placebo-treated patients.[104] Additional studies are currently being conducted to assess potential long-term adverse effects.

5. Conclusion

Although urinary incontinence is common and troublesome, fewer than half of the women with urinary incontinence seek medical care. Instead, they rely on absorbent pads or lifestyle changes to cope with the condition. Although it is uncertain why so few women with this problem consult a physician, the absence of a widely indicated pharmacological option and the patient's belief that incontinence cannot be treated without invasive surgery certainly play an important role.

The pharmacological treatment of SUI aims at increasing intraurethral pressure by increasing tone in the urethral smooth muscle or by affecting tone of the striated muscles in the urethra and pelvic floor. Several drugs have been used off-label to effect these changes, but the results have been largely disappointing, partly as a result of inconsistent treatment efficacy, but mainly because of serious adverse reactions. The use of many of these pharmacological agents is based more on tradition than on evidence from large, controlled clinical trials.

In recent years, studies have uncovered a role for central neurotransmitters in the control of the lower urinary tract, and specific targets for pharmacological intervention have been identified in increasing bladder outlet resistance. Preclinical and early human studies have revealed potential neurological targets for modulating lower urinary tract function; in particular, pharmacotherapies aimed at increasing neural activity to the striated urethral sphincter, or rhabdosphincter, may show promise in reducing the incidence of SUI. One such pharmacological agent – duloxetine – inhibits presynaptic neurone reuptake of serotonin and norepinephrine in the CNS (sacral spinal cord), potentially increasing urethral closure forces and, thereby, reducing episodes of SUI. The efficacy and safety of duloxetine in the treatment of SUI have been demonstrated in phase II and phase III randomised, placebo-controlled trials in over 1700 women. In all trials, the duloxetine-treated patient group had a ≥50% median decrease in IEF that paralleled improvements in quality-of-life domains. Duloxetine has demonstrated long-term safety from its experience in trials in patients with depression, but further study is needed to assess both long-term efficacy and potential long-term adverse effects.

A New Drug Application for duloxetine was filed for SUI to the US FDA in late 2002 and to the EU Committee for Proprietary Medicinal Products in early 2003. If approved, duloxetine could become the first pharmacological treatment widely indicated to reduce the frequency of SUI episodes and could go a long way towards expanding the available treatment options for clinicians. In particular, women who are unable or unwilling to perform pelvic floor muscle training, who are poor candidates for surgery or who wish to postpone or avoid surgery would be excellent candidates for duloxetine. Since urinary incontinence is a growing medical, social and economic problem worldwide, the need for more effective and cost-efficient therapies is critical.

Acknowledgements

Norman R. Zinner serves on an advisory board and has a consulting agreement with Eli Lilly and Company and Boehringer Ingelheim. He has also been an investigator in studies funded by Eli Lilly and Boehringer Ingelheim. Stephanie C. Koke and Lars Viktrup are both full-time employees of Eli Lilly and Company and hold stock and/or stock options in the company. Duloxetine, an investigational drug mentioned in this article, is currently being studied by Eli Lilly and Company and Boehringer Ingelheim.

References

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Am J Obstet Gynecol 2002; 187 (1): 116-26
2. Hunskaar S, Arnold EP, Burgio K, et al. Epidemiology and natural history of urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2000; 11 (5): 301-19
3. Hannestad YS, Rortveit G, Sandvik H, et al. A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT Study. J Clin Epidemiol 2000; 53 (11): 1150-7
4. Koelbl H, Mostwin J, Boiteux JP, et al. Pathophysiology. In: Abrams P, Khoury S, Wein A, editors. Incontinence. Plymouth: Health Publication Ltd, 2002: 205-41
5. Viktrup L. The risk of lower urinary tract symptoms five years after the first delivery. Neurourol Urodyn 2002; 21 (1): 2-29
6. Bump RC, Norton PA. Epidemiology and natural history of pelvic floor dysfunction. Obstet Gynecol Clin North Am 1988; 25: 723-46
7. Viktrup L. Female stress and urge incontinence in family practice: insight into the lower urinary tract. Int J Clin Pract 2002; 56 (9): 694-700
8. Fultz NH, Herzog AR. Self-reported social and emotional impact of urinary incontinence. J Am Geriatr Soc 2001; 49 (7): 892-9
9. Brown JS, Vittinghoff E, Wyman JF, et al. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc 2000; 48 (7): 721-5
10. Thom DH, Haan MN, Van Den Eeden SK. Medically recognized urinary incontinence and risks of hospitalization, nursing home admission and mortality. Age Ageing 1997; 26 (5): 367-74
11. Wilson L, Brown JS, Shin GP, et al. Annual direct cost of urinary incontinence. Obstet Gynecol 2001; 98 (3): 398-406
12. Berglund A, Fugl-Meyer K. Some sexological characteristics of stress incontinent women. Scand J Urol Nephrol 1996; 30 (3): 207-12
13. Fultz NH, Burgio K, Diokno AC, et al. Burden of stress urinary incontinence for community-dwelling women. Am J Obstet Gynecol 2003; 189 (5): 1275-82
14. Wagner TH, Hu TW. Economic costs of urinary incontinence in 1995. Urology 1998; 51 (3): 355-61
15. Wall L, Norton PA, DeLancey JO. Absorbent products and catheters. Baltimore (MD): Williams and Wilkins, 1993
16. Kinchen KS, Bump RC, Gohier J. Prevalence and frequency of stress urinary incontinence among community-dwelling women [abstract]. Eur Urol Suppl 2002; 1 (1): 85
17. Dugan E, Roberts CP, Cohen SJ, et al. Why older community-dwelling adults do not discuss urinary incontinence with their primary care physicians. J Am Geriatr Soc 2001; 49 (4): 462-5
18. Cheater FM, Castleden CM. Epidemiology and classification of urinary incontinence. Baillieres Best Pract Res Clin Obstet Gynaecol 2000; 14 (2): 183-205
19. Thom D. Variation in estimates of urinary incontinence prevalence in the community: effects of differences in definition, population characteristics, and study type. J Am Geriatr Soc 1998; 46 (4): 473-80
20. Cammu H, Van Nylen M, Amy JJ. A 10-year follow-up after Kegel pelvic floor muscle exercises for genuine stress incontinence. BJU Int 2000; 85 (6): 655-8
21. Bo K. Pelvic floor muscle exercise for the treatment of genuine stress incontinence: an exercise physiology perspective. Int Urogynecol J 1995; 6: 282-91
22. Morkved S, Bo K. Effect of postpartum pelvic floor muscle training in prevention and treatment of urinary incontinence: a one-year follow up. Br J Obstet Gynecol 2000; 107 (8): 1022-8
23. Ashworth PD, Hagan MP. Some social consequences of non-compliance with pelvic floor exercises. Physiotherapy 1993; 79: 465-71
24. Burns B, Pranikoff K, Nochajski T, et al. A comparison of effectiveness of biofeedback and pelvic muscle exercise treatment of stress incontinence in older community-dwelling women. J Gerontol Med Sci 1993; 48: M167-74
25. Lapitan MC, Cody DJ, Grant AM. Open retropubic colposuspension for urinary incontinence in women. Cochrane Database Syst Rev 2003; (1): CD002912
26. Bezerra CA, Bruschini H. Suburethral sling operations for urinary incontinence in women. Cochrane Database Syst Rev 2000; (3): CD001754. Update in: Cochrane Database Syst Rev 2001; (3): CD001754
27. Nilsson CG, Kuuva N, Falconer C, et al. Long-term results of the tension-free vaginal tape (TVT) for surgical treatment of female stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2001; 12 Suppl. 2: S5-8
28. Hilton P. Trials of surgery for stress incontinence: thoughts on the 'Humpty Dumpty principle'. Br J Obstet Gynecol 2002; 109 (10): 1081-8
29. Black NA, Downs S. The effectiveness of surgery for stress incontinence in women: a systematic review. Br J Urol 1996; 78: 497-510
30. Herschorn S. Current status of injectable agents for female stress urinary incontinence. Can J Urol 2001; 8 (3): 1281-9
31. Burkhart KS. Urinary incontinence in women: assessment and management in the primary care setting. Nurse Pract Forum 2000; 11 (4): 192-204
32. Andersson K-E, Appell R, Awad S, et al. Pharmacological treatment of urinary incontinence. In: Abrams P, Khoury S, Wein A, editors. Incontinence. Plymouth: Health Publications Ltd, 2002: 481-511
33. Abrams P, Khoury S, Wein A, editors. Incontinence (2nd International Consultation on Incontinence, WHO). Plymouth: Health Publications Ltd, 2002
34. Versi E, Cardozo L. Estrogens and the lower urinary tract function. London: Blackwell Scientific, 1988
35. Hodgson BJ, Dumas S, Bolling DR, et al. Effect of estrogen on sensitivity of rabbit bladder and urethra to phenylephrine. Invest Urol 1978; 16 (1): 67-9
36. Larsson B, Andersson K, Batra S, et al. Effects of estradiol on norepinephrine-induced contraction, alpha adrenoceptor number and norepinephrine content in the female rabbit urethra. J Pharmacol Exp Ther 1984; 229: 557-63
37. Bump RC, Friedman CI. Intraluminal urethral pressure measurements in the female baboon: effects of hormonal manipulation. J Urol 1986; 136 (2): 508-11
38. Hextall A. Oestrogens and lower urinary tract function. Maturitas 2000; 36 (2): 83-92
39. Fantl JA, Bump RC, Robinson D, et al. Efficacy of estrogen supplementation in the treatment of urinary incontinence: the Continence Program for Women Research Group. Obstet Gynecol 1996; 88 (5): 745-9
40. Jackson DA, Shepherd A, Abrams P. The effect of oestradiol on objective urinary leakage in postmenopausal stress inconti-

nence: a double blind placebo control trial [abstract]. Neurourol Urodyn 1996; 15: 322
41. Blakeman PJ, Hilton P, Bulmer JN. Cellular proliferation in the female lower urinary tract with reference to oestrogen status. BJOG 2001; 108 (8): 813-6
42. Fantl JA, Cardozo L, McClish DK. Estrogen therapy in the management of urinary incontinence in postmenopausal women: a meta-analysis. First report of the Hormones and Urogenital Therapy Committee. Obstet Gynecol 1994; 83 (1): 12-8
43. Sultana C, Walters M. Estrogen and urinary incontinence in women. Maturitas 1990; 20: 129-38
44. Al-Badr A, Ross S, Soroka D, et al. What is the available evidence for hormone replacement therapy in women with stress urinary incontinence? J Obstet Gynaecol Can 2003; 25 (7): 567-74
45. Moehrer B, Hextall A, Jackson S. Oestrogens for urinary incontinence in women. Cochrane Database Syst Rev 2003 (2): CD001405
46. Grady D, Brown JS, Vittinghoff E, et al. Postmenopausal hormones and incontinence: the Heart and Estrogen/Progestin Replacement Study. Obstet Gynecol 2001; 97 (1): 116-20
47. Rodriguez C, Patel AV, Calle EE, et al. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. JAMA 2001; 285 (11): 1460-5
48. Porch J, Lee IM, Cook NR, et al. Estrogen-progestin replacement therapy and breast cancer risk: the Women's Health Study (United States). Cancer Causes Control 2002; 13 (9): 847-54
49. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003; 289 (24): 3243-53
50. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003; 362 (9382): 419-27
51. Goode PS, Burgio KL. Pharmacologic treatment of lower urinary tract dysfunction in geriatric patients. Am J Med Sci 1997; 314 (4): 262-7
52. Brune ME, O'Neill AB, Gauvin DM, et al. Comparison of alpha 1-adrenoceptor agonists in canine urethral pressure profilometry and abdominal leak point pressure models. J Urol 2001; 166 (4): 1555-9
53. Diokno AC, Taub M. Ephedrine in treatment of urinary incontinence. Urology 1975; 5 (5): 624-5
54. Awad SA, Downie JW, Kiruluta HG. Alpha-adrenergic agents in urinary disorders of the proximal urethra: part I. Sphincteric incontinence. Br J Urol 1978; 50 (5): 332-5
55. Ek A, Andersson KE, Gullberg B, et al. The effects of long-term treatment with norephedrine on stress incontinence and urethral closure pressure profile. Scand J Urol Nephrol 1978; 12 (2): 105-10
56. Collste L, Lindskog M. Phenylpropanolamine in treatment of female stress urinary incontinence: double-blind placebo controlled study in 24 patients. Urology 1987; 30 (4): 398-403
57. Siltberg H, Larsson G, Hallen B, et al. Validation of cough-induced leak point pressure measurement in the evaluation of pharmacological treatment of stress incontinence. Neurourol Urodyn 1999; 18 (6): 591-602
58. Beisland HO, Fossberg E, Moer A, et al. Urethral sphincteric insufficiency in postmenopausal females: treatment with phenylpropanolamine and estriol separately and in combination: a urodynamic and clinical evaluation. Urol Int 1984; 39 (4): 211-6
59. Hilton P, Tweddel A, Mayne C. Oral and intravaginal estrogens alone and in combination with alpha adrenergic stimulation in genuine stress incontinence. Int Urogynecol J 1990; 12: 80-6
60. Fleming G. The FDA, regulation, and the risk of stroke. N Engl J Med 2000; 343: 1886-7
61. Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. N Engl J Med 2000; 343 (25): 1826-32
62. Weil EH, Eerdmans PH, Dijkman GA, et al. Randomized double-blind placebo-controlled multicenter evaluation of efficacy and dose finding of midodrine hydrochloride in women with mild to moderate stress urinary incontinence: a phase II study. Int Urogynecol J Pelvic Floor Dysfunct 1998; 9 (3): 145-50
63. Radley SC, Chapple CR, Bryan NP, et al. Effect of methoxamine on maximum urethral pressure in women with genuine stress incontinence: a placebo-controlled, double-blind crossover study. Neurourol Urodyn 2001; 20 (1): 43-52
64. Gatti JM, Perez-Brayfield M, Kirsch AJ, et al. Acute urinary retention in children. J Urol 2001; 165 (3): 918-21
65. Andersson KE. Neurotransmission and drug effects in urethral smooth muscle. Scand J Urol Nephrol Suppl 2001; (207): 26-34
66. Nasu K, Moriyama N, Fukasawa R, et al. Quantification and distribution of alpha1-adrenoceptor subtype mRNAs in human proximal urethra. Br J Pharmacol 1998; 123 (7): 1289-93
67. Ishiko O, Ushiroyama T, Saji F, et al. Beta (2)-adrenergic agonists and pelvic floor exercises for female stress incontinence. Int J Gynaecol Obstet 2000; 71 (1): 39-44
68. Yasuda K, Kawabe K, Takimoto K. A double-blind clinical trial of a β2-adrenergic agonist in stress incontinence [abstract]. Int Urogynecol J 1993; 4: 146
69. Noguchi M, Eguchi Y, Ichiki J, et al. Therapeutic efficacy of clenbuterol for urinary incontinence after radical prostatectomy. Int J Urol 1997; 4 (5): 480-3
70. Gleason DM, Reilly RJ, Bottaccini MR, et al. The urethral continence zone and its relation to stress incontinence. J Urol 1974; 112 (1): 81-8
71. Kaisary AV. Beta adrenoceptor blockade in the treatment of female urinary stress incontinence. J Urol (Paris) 1984; 90 (5): 351-3
72. Rovner ES, Wein A. Drug treatment of voiding dysfunction. 1st ed. London: Isis Medical Media, 2001
73. Gilja I, Radej M, Kovacic M, et al. Conservative treatment of female stress incontinence with imipramine. J Urol 1984; 132 (5): 909-11
74. Lin HH, Sheu BC, Lo MC, et al. Comparison of treatment outcomes for imipramine for female genuine stress incontinence. Br J Obstet Gynaecol 1999; 106 (10): 1089-92
75. Woodman PJ, Misko CA, Fischer JR. The use of short-form quality of life questionnaires to measure the impact of imipramine on women with urge incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2001; 12 (5): 312-5
76. Frazer A. Pharmacology of antidepressants. J Clin Psychopharmacol 1997; 17 Suppl. 1: 2S-18S
77. Khullar V, Digesu A, Chaliha C, et al. Mixed incontinence: how should it be treated? Neurourol Urodyn 2002; 21 (4): 378-9
78. Espey MJ, Du HJ, Downie JW. Serotonergic modulation of spinal ascending activity and sacral reflex activity evoked by pelvic nerve stimulation in cats. Brain Res 1998; 798 (1-2): 101-8
79. Thor KB, Hisamitsu T, de Groat WC. Unmasking of a neonatal somatovesical reflex in adult cats by the serotonin autoreceptor

agonist 5-methoxy-N,N-dimethyltryptamine. Brain Res Dev Brain Res 1990; 54 (1): 35-42

80. Danuser H, Thor KB. Spinal 5-HT2 receptor-mediated facilitation of pudendal nerve reflexes in the anaesthetized cat. Br J Pharmacol 1996; 118 (1): 150-4

81. Gajewski J, Downie JW, Awad SA. Experimental evidence for a central nervous system site of action in the effect of alpha-adrenergic blockers on the external urinary sphincter. J Urol 1984; 132 (2): 403-9

82. Espey MJ, Downie JW, Fine A. Effect of 5-HT receptor and adrenoceptor antagonists on micturition in conscious cats. Eur J Pharmacol 1992; 221 (1): 167-70

83. Bae JH, Moon DG, Lee JG. The effects of a selective noradrenaline reuptake inhibitor on the urethra: an *in vitro* and *in vivo* study. BJU Int 2001; 88 (7): 771-5

84. Votolato NA, Stern S, Caputo RM. Serotonergic antidepressants and urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2000; 11 (6): 386-8

85. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters *in vitro* and *in vivo*, human serotonin receptor subtypes, and other neuronal receptors. Neuropsychopharmacology 2001; 25 (6): 871-80

86. Norton PA, Zinner NR, Yalcin I, et al. Duloxetine versus placebo in the treatment of stress urinary incontinence. Am J Obstet Gynecol 2002; 187 (1): 40-8

87. Dmochowski RR, Miklos JR, Norton PA, et al. Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence. J Urol 2003; 170: 1259-63

88. van Kerrebroeck P, Abrams P, Lange R, et al. Duloxetine vs placebo in the treatment of European and Canadian women with stress urinary incontinence. BJOG 2004; 111: 249-57

89. Nemeroff CB, Schatzberg AF, Goldstein DJ, et al. Duloxetine for the treatment of major depressive disorder. Psychopharmacol Bull 2002; 36: 106-32

90. Wong DT, Bymaster FP, Mayle DA, et al. LY248686, a new inhibitor of serotonin and norepinephrine uptake. Neuropsychopharmacology 1993; 8 (1): 23-33

91. Thor KB, Katofiasc MA. Effects of duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, on central neural control of lower urinary tract function in the chloralose-anesthetized female cat. J Pharmacol Exp Ther 1995; 274 (2): 1014-24

92. Katofiasc MA, Nissen J, Audia JE, et al. Comparison of the effects of serotonin selective, norepinephrine selective, and dual serotonin and norepinephrine reuptake inhibitors on lower urinary tract function in cats. Life Sci 2002; 71 (11): 1227-36

93. Sharma A, Goldberg MJ, Cerimele BJ. Pharmacokinetics and safety of duloxetine, a dual-serotonin and norepinephrine reuptake inhibitor. J Clin Pharmacol 2000; 40 (2): 161-7

94. Skinner MH, Kuan HY, Pan A, et al. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. Clin Pharmacol Ther 2003; 73 (3): 170-7

95. diVirgilio S, Gonzales C, Knadler M, et al. Effect of duloxetine (DU) on CYP1A2-mediated drug metabolism and the pharmacokinetics (PK) of theophylline (THEO) [abstract]. Clin Pharmacol Ther 2002; 71 (2): 63

96. Chalon SA, Granier LA, Vandenhende FR, et al. Duloxetine increases serotonin and norepinephrine availability in healthy subjects: a double-blind, controlled study. Neuropsychopharmacology 2003; 28 (9): 1685-93

97. Sathirakul K, Teng L, Yeo K, et al. Impact of gastric pH and the presence of activated charcoal on the absorption of duloxetine [abstract]. Clin Pharmacol Ther 2002; 71 (2): 18

98. Bump R, Hooper C, Koke S, et al. Worldwide efficacy of duloxetine after 12 weeks and 1 year in women with stress urinary oncontinemce (SUI): a 4-study meta-analysis [abstract no. 337]. 33rd Annual International Continence Society Meeting; 2003 Oct 5-9; Florence

99. Dubeau CE, Khullar V. Drug impact on the SUI component of mixed incontinence: is it all placebo effect? [abstract]. American Urogynecologic Society Meeting; 2002 Oct 16-19; San Francisco

100. Ramsay IN, Thou M. A randomised, double-blind, placebo controlled trial of pelvic floor exercises in the treatment of genuine stress incontinence. Neurourol Urodyn 1990; 9: 398-9

101. Bailar III JC. The powerful placebo and the wizard of Oz. N Engl J Med 2001; 344: 1630-2

102. Mallinckrodt C, Goldstein DJ, Detke MJ, et al. Duloxetine: a new treatment for the emotional and physical symptoms of depression. Primary Care Companion J Clin Psych 2003; 5: 19-28

103. Raskin J, Goldstein DJ, Mallinckrodt C, et al. Duloxetine in the long-term treatment of major depressive disorder [poster]. Presented at the US Psychiatric and Mental Health 15th Annual Congress; 2002 Oct 28-31; Las Vegas

104. Brannan S, Detke MJ, Wang F, et al. Comparison of sexual functioning in patients receiving duloxetine or paroxetine: acute- and long-term data [poster]. Presented at the American Psychiatric Association 156th Annual Meeting; 2003 May 17-22; San Francisco

Correspondence and offprints: Dr *Norman R. Zinner*, Western Clinical Research, Inc., 23441 Madison Street, Suite 130, Torrance, CA 90505, USA.
E-mail: wewedoc@aol.com