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Duloxetine

A Viewpoint by Richard J. Millard

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Stress urinary incontinence (SUI) is caused by weakness of the urethral sphincter mechanism which consists of smooth muscle, striated muscle and connective and vascular tissue. Hypermobility of the urethra may or may not coexist and may require surgical correction. Pelvic muscle exercises have been the mainstay of conservative treatment of SUI since Kegel popularised them over half a century ago.

Until the advent of duloxetine, there was no pharmacological agent that could be used for the treatment of patients with SUI. α-Adrenergic agents such as pseudoephedrine have been used to stimulate urethral resistance by increasing smooth muscle tone, but tachyphylaxis and adverse effects make them virtually useless. In addition, alpha stimulation of the smooth muscle component of urethral resistance can produce voiding difficulty, for example, when older men develop acute urinary retention after taking medication for the common cold.

Duloxetine, by contrast, is thought to exert its action by facilitation of the continence pathway to the rhabdosphincter at the level of Onuf's nucleus in the sacral cord. Thus, only the striated muscle component of urethral resistance is stimulated during the storage phase of bladder filling. It has no effect on the voiding phase of bladder emptying, wherein the rhabdosphincter relaxes by a different neural pathway, and therefore has no effect on voiding efficiency. In addition, urethral striated muscle is more effective than urethral smooth muscle in increasing urethral resistance, both at rest and during reflex guarding reflexes that are invoked by raised intra-abdominal pressure during the coughing, sneezing, lifting and similar activities which induce SUI.

At a dose of 40mg twice daily, duloxetine has been shown to be effective in treating women with SUI. It also augments the effects of pelvic floor muscle exercises, which most women are encouraged to do for 3–6 months before recourse to stress incontinence surgery. Nausea is usually early, mild and transient, but some women will drop out before the benefit in improved SUI is apparent.

Duloxetine is likely to find a place in the treatment of SUI in women at the early stage of presentation to the primary care physician (PCP). Previously this group has been content to refer their patients on to gynaecologists or urologists for diagnosis and treatment, mainly because there was nothing for the PCP to prescribe. This is about to change as new drugs become available for both SUI and overactive bladder (e.g. selective antimuscarinics); the PCP will be educated and empowered to deliver primary therapy without specialist referral. At present, only 30% of incontinent people ever seek help. However, public education campaigns by pharmaceutical companies and continence promotion organisations will persuade more people to seek help at an earlier stage when drug therapy is most likely to be effective.

Specialist use of duloxetine is likely to be in women awaiting surgery for SUI, or those unfit for surgery. It will not supplant surgical correction of hypermobility or pelvic organ prolapse. However, some conservative therapies used for SUI, including vaginal devices (e.g. Introl, Contiform or ring pessaries), may be more effective when combined with duloxetine. Further trials will be needed to establish the true value of these combinations.

The benefit of duloxetine in post-prostatectomy incontinence in men is also yet to be proven. It is likely to be used as first-line therapy (combined with pelvic floor muscle exercises) by urologists confronted by an incontinent man after either transurethral resection of the prostate or radical prostatectomy (possibly in off-label use well before any trials are published).

Whether it is possible that duloxetine, by stimulation of the rhabdosphincter during bladder filling, can reduce detrusor overactivity and thereby improve the symptoms of the overactive bladder syndrome (frequency, urgency and nocturia with or without urge incontinence) is still the subject of further trials. These must surely compare duloxetine with standard antimuscarinic therapy for this condition if they are to be credible. ▲