

Duloxetine

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Stress urinary incontinence (SUI) therapy has been devoid of novel pharmacologic strategies to increase urethral resistance. Although drugs with α -adrenergic agonist activity have been used to treat SUI, none are approved by the FDA. Emerging pharmacological options may offer the possibility of a new approach to first-line therapy for SUI.

In the search for drugs to treat SUI, animal studies have been conducted with various norepinephrine-selective, serotonin-selective, or dual serotonin and norepinephrine (noradrenaline) reuptake inhibitors. The administration of serotonin 5-HT₂ agonists produces a marked increase in the amplitude of the sphincter reflex. Administering a 5-HT₂ antagonist reverses these effects, suggesting that stimulation of 5-HT₂ receptors enhances guarding reflexes and could improve continence. Selective α_1 -adrenergic receptor antagonists can decrease the amplitude of sphincteric reflexes, indicating that a selective norepinephrine agonist would be a logical pharmaceutical target to facilitate urethral continence.

The effect of duloxetine on neural control of the lower urinary tract has been investigated in cats and rats. Studies demonstrated that duloxetine significantly increased sphincter electromyographic activity. Dual serotonergic and noradrenergic reuptake inhibitors prolong serotonin and norepinephrine neurotransmitters in the synaptic cleft, thereby increasing receptor stimulation. The ability of duloxetine to increase the activity of the sphincter muscle function makes this an attractive compound in the treatment of SUI.

Duloxetine has several advantages. Firstly, once approved, it will be the only drug available to treat this common and bothersome condition. Secondly, the efficacy data are significantly positive across all of the studies conducted throughout the world. Thirdly, duloxetine can be used in conjunction with traditional pelvic floor exercise, and has synergistic activity when combined with these exercises. Fourthly, the agent is helpful for both mild and severe forms of SUI and can be used prior to considering bladder suspension surgery. In such cases, duloxetine can delay or even nullify the need for surgery.

Duloxetine also has disadvantages. Firstly, there are adverse effects, especially nausea. The discontinuation rate for adverse events attributable to duloxetine is about 16%, with nausea being the most common reason for discontinuation. However, most of the adverse effects occur within the first 2 weeks and then subside. Secondly, there will be some confusion in the market place. Duloxetine is approved in the US for the treatment of depression and diabetic neuropathic pain, using a different dose and under a different trade name to that for SUI. Therefore, education of healthcare providers will be important to avoid two doctors prescribing the same chemical twice, at different doses for depression and SUI.

In conclusion, advances in the basic understanding of the neurourology of lower urinary tract function have fueled investigation into new pharmacological strategies to treat SUI. Duloxetine, a dual serotonin-norepinephrine reuptake inhibitor, has demonstrated the ability to reduce incontinence frequency and improve quality of life in multiple international clinical trials of women with SUI. Duloxetine will be the first and only drug available to help women with SUI. ▲