Duloxetine: A New Pharmacologic Therapy for Stress Urinary Incontinence

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The dual serotonin (5-HT)/norepinephrine (NE) reuptake inhibitor duloxetine shows promise as a pharmacologic therapy for stress urinary incontinence. This agent modulates lower urinary tract function through selective inhibition of 5-HT and NE receptor sites. It works centrally at Onuf's nucleus to increase activity of the pudendal nerve. Duloxetine facilitates sphincter activity during urine storage but not during voiding, maintaining the bladder-sphincter synergy. Because it inhibits both 5-HT and NE reuptake, duloxetine appears to offer an advantage over agents that inhibit reuptake of a single neurotransmitter.
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Key words: Duloxetine • Serotonin • Norepinephrine • Stress urinary incontinence

In recent years, there has been an increased emphasis on the pharmacologic treatment of urinary incontinence. For the most part, this interest has been focused on the development of new compounds and formulations for the treatment of urge incontinence. Theoretically, however, stress urinary incontinence (SUI) should also respond to pharmacologic therapy and, indeed, some medications have been shown to provide symptom relief for women with SUI.[1]

Physiologically, the muscle tone of the urethra and bladder neck are maintained by α-adrenergic activity from the sympathetic nervous system. α-Agonists have been used to treat SUI with modest, at best, success. Most clinical trials, however, have focused on the use of phenylpropanolamine, an agent that was recently withdrawn from the market by the Food and Drug Administration because of an associated increased risk of stroke and cardiovascular toxicity.[2] Other α-agonists, such as ephedrine and pseudoephedrine, have not been adequately studied, and most experts agree that their effects on SUI are minimal. Furthermore, ephedra alkaloids may all be associated with the same adverse effects as phenylpropanolamine, including risk of hypertension, seizures, and stroke.[3]

Imipramine has been used to treat SUI. This agent has anticholinergic and sedative properties and acts as an inhibitor of norepinephrine (NE) and serotonin (5-HT). The effect of imipramine on SUI has been studied in 2 open-label trials, both of which demonstrated some therapeutic benefit.[4,5] However, relatively high dosages (75 mg/d) were used, at which significant side effects are common. No randomized, controlled studies of imipramine for the treatment of SUI have been conducted. This lack of data, toxicity information, and clinical experience with imipramine limits its role in the treatment of SUI.

Estrogen replacement therapy has been demonstrated to reduce complaints of urgency, frequency, and vaginal dryness. A plethora of information exists regarding estrogen replacement for the treatment of incontinence in general and SUI specifically. A number of recent critical reviews suggest that the role of estrogen in the treatment of SUI is limited at best.[6-8]

Recent advances in our understanding of the neurophysiology of the lower urinary tract have prompted research into new pharmacologic therapies for SUI. One such agent is duloxetine, which is a balanced and potent inhibitor of 5-HT and NE reuptake. This agent's unique mechanism of action and effect on the lower urinary tract make it an intriguing compound for use in women with SUI.

Duloxetine for the Treatment of SUI

Duloxetine ([+]-[S]-*N*-methyl-γ-[1-naphthalenyloxy]-2-thiophenepropanamine hydrochloride) (Figure 1) is a potent dual reuptake inhibitor of NE and 5-HT that has been studied for the treatment of SUI. Compared with similar agents, duloxetine achieves a relatively evenly balanced inhibition of NE and 5-HT, which likely contributes to its efficacy in treating SUI. The compound also possesses weak activity on dopamine reuptake.[9,10]

Duloxetine has no significant affinity for α-adrenergic, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, muscarinic, histamine H1, dopamine D2, or opioid receptors. By blocking the reuptake of NE and 5-HT from presynaptic serotonergic (or adrenergic) nerve terminals, duloxetine allows the postsynaptic receptors to be continually stimulated by 5-HT or NE (Figure 2). This is particularly important in Onuf's nucleus in the sacral spinal cord, because postsynaptic nerves arising here innervate the striated urethral sphincter. Human and animal studies have also demonstrated that duloxetine increases the release of 5-HT and NE in the limbic areas of the brain and, under irritated bladder condi-

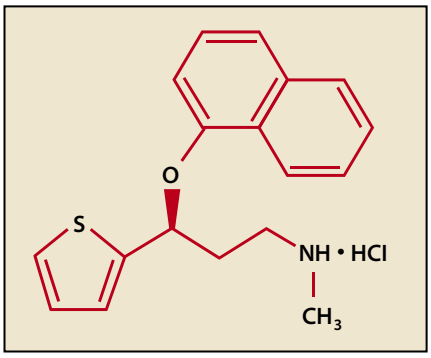
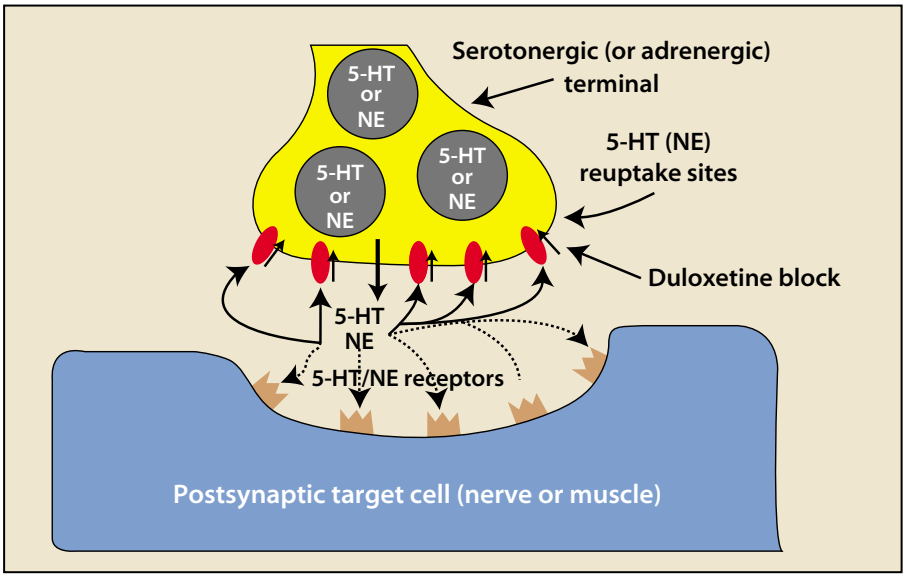


Figure 1. *The molecular structure of duloxetine ([+]-[S]-N-methyl-γ-[1-naphthalenyloxy]-2-thiophenepropanamine hydrochloride): $C_{18}H_{19}NOS$•HCl (molecular weight, 333.88).*

Figure 2. *Duloxetine blocks norepinephrine (NE) and serotonin (5-HT) reuptake and increases receptor activation.*



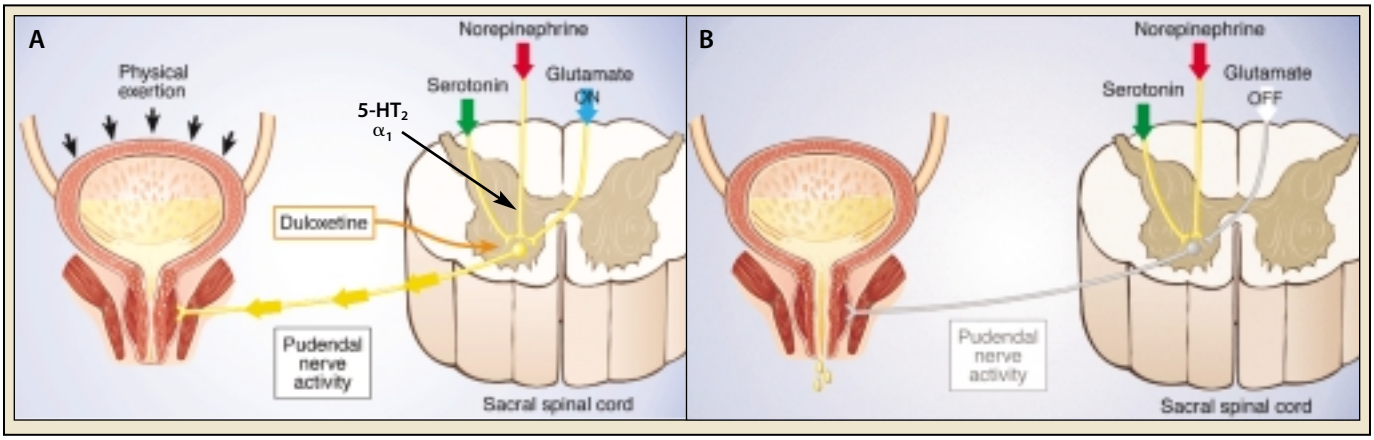


Figure 3. **(A)** *Urine storage: The neurotransmitter glutamate, which is present during urine storage, is necessary for the stimulatory effect of serotonin (5-HT) and norepinephrine (NE) on the pudendal nerve. Duloxetine, by its inhibition of 5-HT and NE reuptake, enhances this stimulation.* **(B)** *Voiding: During the voiding phase, glutamate transmission is turned off; thus, the stimulatory effects of 5-HT and NE (and enhancement of this effect by duloxetine) are no longer experienced.*

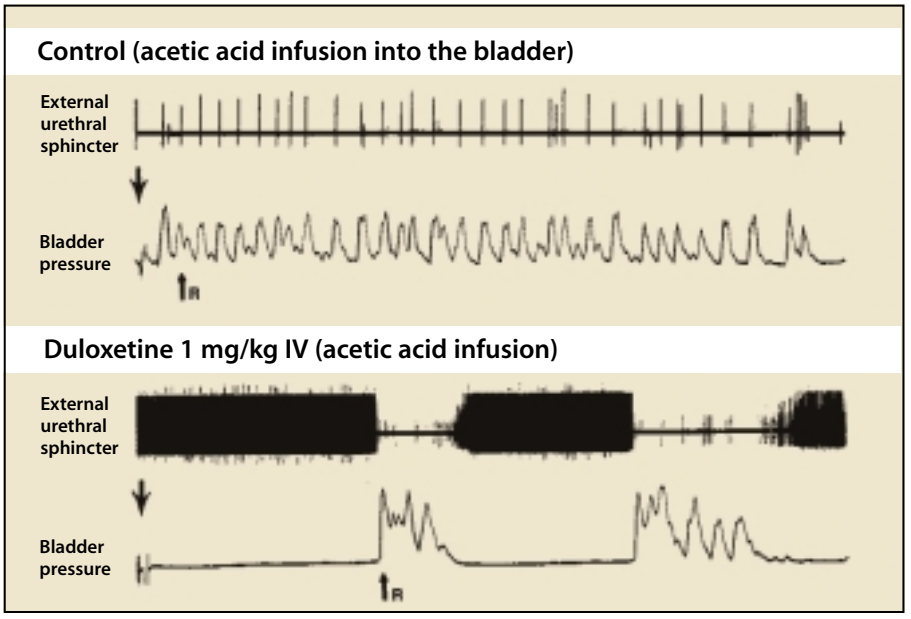
tions, increases bladder capacity and periurethral sphincter activity.[11-13]

Mechanism of Action

Neurologic studies in humans and animal models have demonstrated that monoamine neurotransmitters perform a key function in controlling bladder storage and urinary reflexes.[14] The motor neurons located in Onuf's nucleus in the sacral spinal cord are responsible for innervation of the striated external urethral sphincter (EUS) and, to a large extent, for control of urethral function via postsynaptic nerves to the pudendal nerve. These neuronal pathways have unique properties that distinguish them from other motor neurons: they are uniformly smaller than the surrounding motor neurons and possess bundled dendrites, which are responsible for strong synchronous activation or inhibition. They also have unique neurochemical profiles: unlike motor neurons in the surrounding tissues, those in the Onuf's nucleus have a higher density of serotonergic and noradrenergic terminals. Studies have demonstrated that the α_1-adrenoceptors and 5-HT receptors within Onuf's nucleus facilitate EUS contraction.[15-19]

Investigators have demonstrated that sphincter neuron activity can be enhanced pharmacologically during urine storage without disrupting the synergy between bladder storage and urethral sphincter activity.[20] This is possible primarily because of the "on/off switch" mediated by the neurotransmitter glutamic acid (glutamate). While the pudendal nerve is receiving excitatory glutamatergic transmission, EUS contractions continue and the lower urinary tract remains in the storage mode. Suppression of glutamatergic transmission serves as the final signal for EUS relaxation and bladder emptying. Thus, the effects of duloxetine—that is, 5-HT and NE reuptake inhibition resulting in increased pudendal nerve stimulation—should be evident during storage only (Figure 3). This

Figure 4. *In Thor's anesthetized cat model, acetic acid infusion was used as an irritant to increase bladder activity. Duloxetine administration significantly increased sphincter activity during storage but decreased sphincter activity during voiding (R). Duloxetine also suppressed bladder activity in this model. IV, intravenous. Adapted, with permission, from Thor KB, Katofiasc MA.* J Pharmacol Exp Ther. *1995;274:1014-1024.*[21]



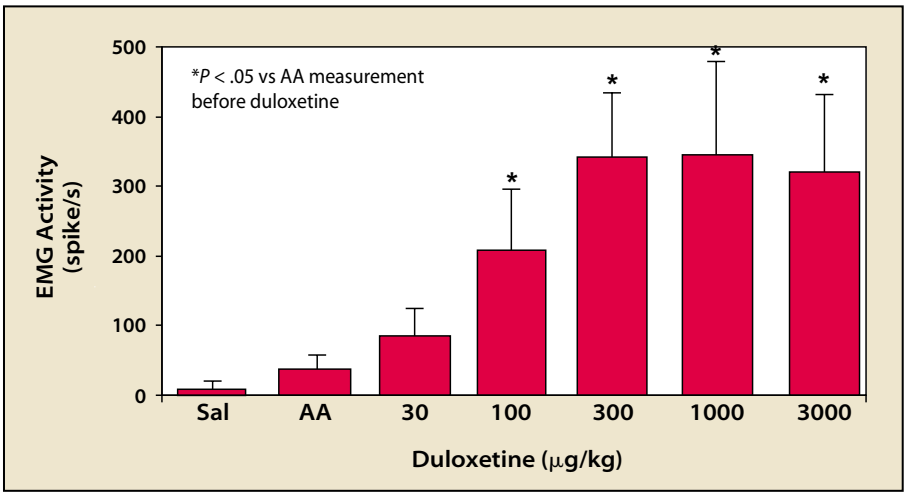


Figure 5. *The effect of duloxetine on external urethral sphincter activity in the cat model is dose-dependent from 30 μg/kg to 300 μg/kg. EMG, electromyographic; Sal, saline; AA, acetic acid. Reproduced, with permission, from Thor KB, Katofiasc MA.* J Pharmacol Exp Ther. *1995;274:1014-1024.*[21]

effect has, in fact, been demonstrated in animal studies.[21]

The classic study demonstrating the effects of duloxetine on lower urinary tract function was performed in the anesthetized cat. Under conditions of acetic acid infusion into the feline bladder, duloxetine was shown to facilitate sphincter activity during storage but not during urination, as well as to suppress bladder activity (Figure 4). The stimulatory effect of duloxetine on EUS function was a dose-dependent phenomenon (Figure 5).[21]

The effects of duloxetine on EUS function in women with SUI have been demonstrated in several phase 2 and phase 3 clinical trials: duloxetine reduces the number of incontinence episodes and improves quality of life in women with SUI, while demonstrating a favorable safety and side-effect profile. Safety and efficacy data from the duloxetine clinical trials are summarized elsewhere in this supplement (see Dmochowski, p. S56).

Pharmacokinetics and Safety

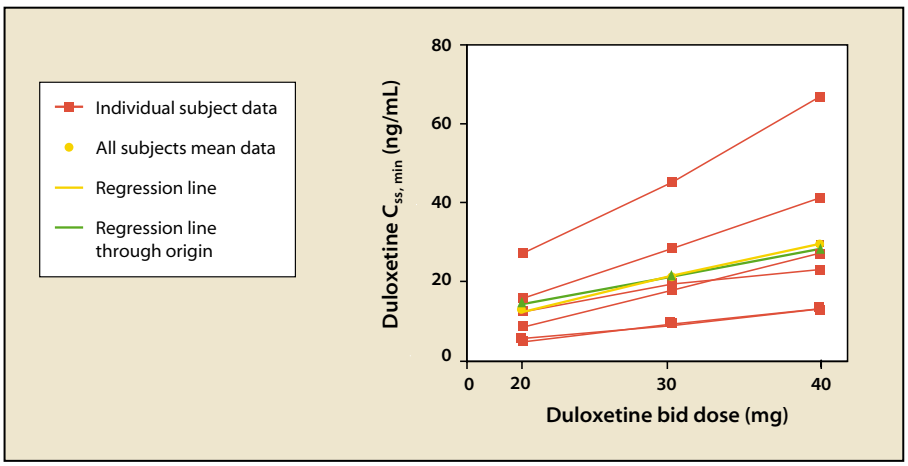
Studies in humans have established that duloxetine exerts its effect via inhibition of 5-HT and NE transporters. In a recent double-blind, controlled study involving healthy participants, cardiovascular and urinary outcome measures suggested that duloxetine affects NE synthesis and turnover, indicating NE reuptake inhibition.[22]

The pharmacokinetic properties of duloxetine were studied in a single-blind, placebo-controlled, escalating multiple-dose trial in 12 healthy adult male volunteers.[23] Subjects in the treatment group (n = 8) received orally administered duloxetine at an initial dosage of 20 mg bid; the dosage was escalated at weekly intervals to 30 mg bid and, finally, to 40 mg bid. Duloxetine demonstrated linear pharmacokinetics with respect to dosage (20-40 mg bid), with a half-life of 12.5 hours; plasma concentrations reached steady state within 3 days (Figure 6).

Following the initial dose, reported side effects included dry mouth, nausea, and somnolence; however, these complaints resolved with continuing administration. Duloxetine was generally well tolerated by all study participants and was not associated with changes in blood pressure or heart rate in the standing position. There were no clinically significant changes noted in electrocardiographic studies, cardiac intervals, neurologic parameters, or routine laboratory assays.[23] Based on the results of early clinical trials, it appears that a minimal plasma concentration is needed for effective around-the-clock treatment of SUI. Based on the current duloxetine delivery system, this is best achieved with twice-daily dosing.

The pharmacokinetics of duloxetine were further studied in a trial conducted by Lantz and colleagues.[11] In this study, drug half-life and elim-

Figure 6. *Pharmacokinetics of duloxetine: mean steady-state plasma trough concentration ($C_{ss,\,min}$) versus duloxetine dose. Reproduced, with permission, from Sharma A et al.* J Clin Pharmacol. *2000;40:161-167.*[23]



ination were assessed in 4 healthy subjects, each of whom received a single 20.2-mg (100.6 μCi) oral dose of isotope-labeled [^{14}C]duloxetine. The mean total recovery of radioactivity after 312 hours was 90.5%, with 72.0% excreted in the urine (Figure 7). Duloxetine is cleared mainly through its metabolites (97%). The investigators identified numerous metabolites, which were primarily excreted in the urine in conjugated form; all major metabolites were also recovered from the plasma. Following [^{14}C]duloxetine administration, maximum concentrations of both the drug and total radioactivity were reached at a median of 6 hours. Duloxetine accounted for less than 3% of the total circulating radioactivity with respect to area under the curve.[11]

Duloxetine Metabolism

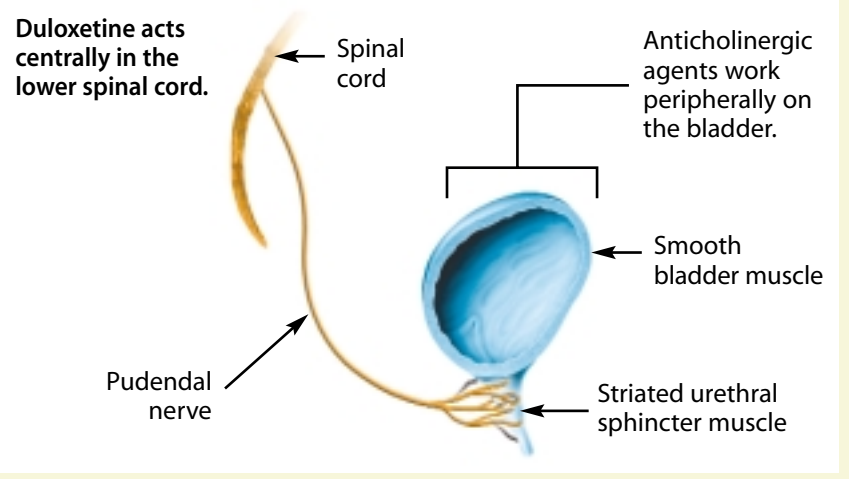
Duloxetine has the potential to act as both an inhibitor and a substrate of the hepatic enzyme cytochrome P450 2D6 (CYP2D6). This enzyme represents a crucial metabolic pathway for a wide variety of medications. Approximately 7% of Caucasians and small number of persons in other ethnic groups carry a genetic polymorphism that can result in a deficiency of CYP2D6. Individuals with this deficiency are referred to as poor metabolizers, whereas those with the wild-type enzyme are designated extensive metabolizers. The pharmacokinetic profiles of drugs that are metabolized primarily by CYP2D6 differ between persons in these 2 genetic groups—a difference that can have consequences on effective drug dosages.[14]

The dual inhibitor/substrate relationship has also been reported for paroxetine, a selective 5-HT reuptake inhibitor. This agent potently inhibits the CYP2D6 hepatic enzyme in a concentration-dependent fashion and can serve as an important metabolic

Duloxetine Works Centrally Rather Than at the Level of the External Sphincter

Many bladder pathologies may be related to disturbances in the central nervous control of the integrated micturition mechanisms, sensory reflex loops, and vesical ganglia. The spinal reflex circuits that are involved in urination exhibit a dense network of serotonergic motor neurons. These nerves are sensitive to serotonin (5-HT) receptor agonists and antagonists, multiple 5-HT receptors, and 5-HT reuptake inhibitors. Stimulation of the serotonergic pathways enhances urine storage by facilitating the vesicosympathetic reflex pathway, while inhibiting the parasympathetic pathways that control urination.

The figure below depicts the spinal cord connections to the pudendal nerve as the activators of both striated urethral sphincter control and bladder smooth muscle control. Duloxetine acts centrally in the lower spinal cord, resulting in stronger urethral sphincter contractions, sustained sphincter tone during urine storage,[1] and virtually no cholinergic receptor affinity,[2,3] whereas anticholinergic agents work peripherally on the bladder to treat urge urinary incontinence and overactive bladder. 5-HT receptor blockers and 5-HT reuptake inhibitors are important compounds in the pharmacologic treatment of detrusor hyperactivity and urinary incontinence. Duloxetine has been demonstrated to modulate bladder function through selective inhibition of both 5-HT and norepinephrine receptor sites.[4-6]



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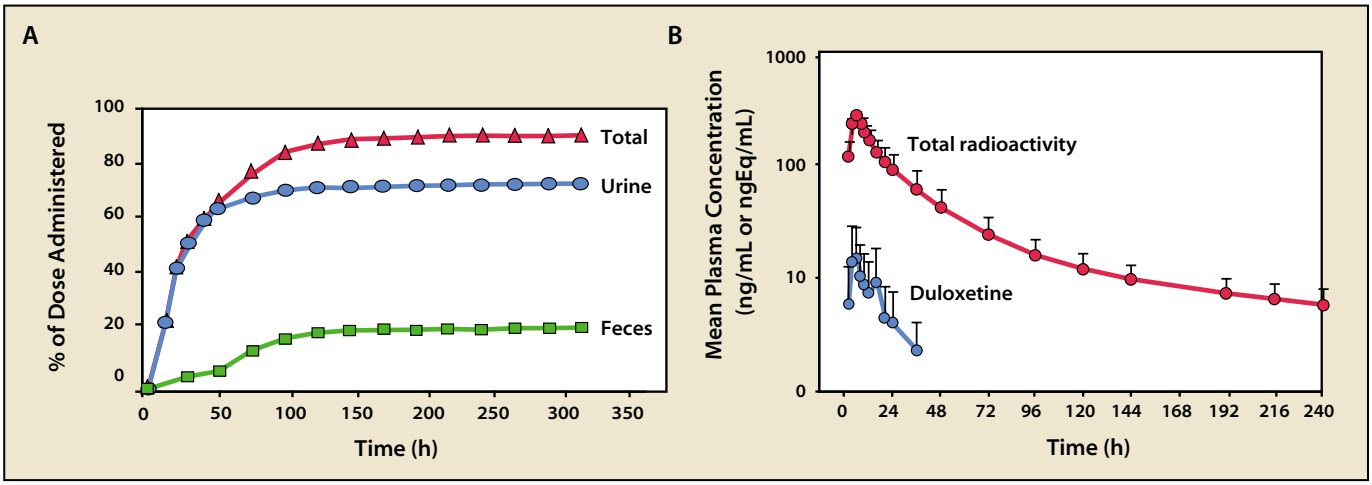

Figure 7. **(A)** *Mean cumulative radioactivity in urine and feces following a single oral 20.2-mg dose of [^{14}C]duloxetine: Duloxetine is excreted primarily (72%) in the urine.* **(B)** *Mean (SD) duloxetine concentration and total radioactivity in plasma following oral administration of [^{14}C]duloxetine: Duloxetine is extensively metabolized and the parent compound is not detectable after 48 hours. Reproduced, with permission, from Lantz RJ et al.* Drug Metabol Dispos. *2003;31:1142-1150.*[11]

model. In a study conducted by Skinner and colleagues,[14] the CYP2D6 activity of paroxetine was shown to have a modest, though statistically significant, influence on the pharmacokinetics of duloxetine. Results demonstrated a 1.6-fold increase in duloxetine plasma exposure at steady state after administration of paroxetine. This moderate increase reflects the availability of alternative pathways for duloxetine metabolism. The alternative metabolic pathway for duloxetine is likely the CYP1A2 enzyme system. Until additional clinical data become available, the coadministration of paroxetine with duloxetine should be closely monitored or avoided entirely.

Because duloxetine is a competitive inhibitor of CYP2D6, it may increase the plasma concentrations of other drugs metabolized by this hepatic enzyme; because it is a substrate of CYP2D6, other competitive inhibitors of this enzyme may increase the plasma concentration of duloxetine. Such drug-drug interactions may or may not be clinically relevant depending on the extent to which plasma concentrations are increased.[14]

Comparative 5-HT and NE Receptor Site Binding Affinities

Studies have shown that other dual 5-HT/NE reuptake inhibitors produce effects on bladder and sphincter function that are qualitatively similar to those of duloxetine. For example, in a study of lower urinary tract function in cats, venlafaxine produced physiologic effects on bladder and sphincter function that were similar to those of duloxetine, despite the structural dissimilarity of the 2 agents. However, the effects of duloxetine were quantitatively an order of magnitude (×10) more potent than those of venlafaxine.[24]

In vitro, duloxetine has been demonstrated to possess a 100-fold or higher affinity for human and animal 5-HT transporters and at least a 300-fold higher affinity for NE transporters compared with venlafaxine. In vivo, duloxetine has been shown to inhibit 5-HT and NE transporter-dependent monoamine depletion by neurotoxins with 2.5-fold and 7.8-fold

Table 1
Inhibition of Binding to Human Monoamine Uptake Transporters

	K_i, nM		
Compound	NE	5-HT	NE/5-HT Ratio
Imipramine	98	19	5.2
Duloxetine	7.5	0.8	9.4
Venlafaxine	2480	82	30
Fluoxetine	1022	7	146
Paroxetine	132	0.4	330
Sertraline	715	0.9	794
Citalopram	>10,000	9.5	>1050

NE, norepinephrine; 5-HT, serotonin.
Data from Bymaster FP et al. *Neuropsychopharmacology.* 2001;25:871-880[10]; Tran PV et al. *J Clin Psychopharmacol.* 2003;23:78-86.[25]

higher potency than venlafaxine, respectively.[10] Thus, venlafaxine has no significant effects on lower urinary tract function in doses administered clinically for the treatment of depression. Other agents used for the treatment of depression, such as fluoxetine, paroxetine, sertraline, and citalopram, are predominately selective 5-HT reuptake inhibitors with little effect on NE reuptake and, thus, have no clinical efficacy for the treatment of SUI (Table 1).[10,25]

Duloxetine's dual 5-HT and NE reuptake inhibition is critical to its effect on lower urinary tract function. In a study conducted by Katofiasc and colleagues,[24] the potent 5-HT reuptake inhibitor s-norfluoxetine produced small increases in sphincter activity and bladder capacity at high doses only. Thionisoxetine, a potent NE reuptake inhibitor, had no effect on sphincter activity or bladder capacity. Moreover, coadministration of s-norfluoxetine and thionisoxetine produced no consistent effect on either parameter. In contrast, the dual inhibitors duloxetine and venlafaxine produced consistent effects on both sphincter activity and bladder capacity, although venlafaxine required doses 10 times higher than those of duloxetine to do so.

Conclusions

Recent developments in the understanding of the neurophysiology of the lower urinary tract have provided new targets for research and development of novel pharmacologic therapies for lower urinary tract dysfunction. One such agent is duloxetine, a potent inhibitor of 5-HT and NE reuptake. This agent has been shown to increase external sphincter electromyographic activity and bladder capacity in animal models. In addition, the safety and efficacy of duloxetine for the treatment of SUI in women has been demonstrated.

Duloxetine's dual inhibition of both 5-HT and NE reuptake appears to offer an advantage over agents that inhibit reuptake of a single neurotransmitter, even when used in conjunction. The relative balance and potency of duloxetine with respect to 5-HT and NE reuptake inhibition make it ideally suited for the treatment of SUI. ■

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Main Points

- The neurons of Onuf's nucleus in the sacral spinal cord are responsible for innervation of the external urethral sphincter and for control of urethral function via postsynaptic nerves to the pudendal nerve. Duloxetine acts centrally in this spinal area to produce stronger urethral sphincter contractions and sustained sphincter tone during urine storage.
- In the anesthetized cat model, duloxetine was shown to facilitate sphincter activity during storage, but not during urination, as well as to suppress bladder activity. The stimulatory effect of duloxetine on EUS function was a dose-dependent phenomenon.
- In a single-blind, placebo-controlled study, duloxetine demonstrated linear pharmacokinetics with respect to dosage (20-40 mg bid), with a half-life of 12.5 hours; plasma concentrations reached steady state within 3 days.
- The dual inhibition of serotonin (5-HT) and norepinephrine (NE) is the key to duloxetine's effectiveness in the treatment of stress urinary incontinence. 5-HT inhibitors and NE inhibitors, alone or combined, have little effect on sphincter activity or bladder capacity.

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