LETTER TO THE EDITORS

Letter

Sirs,

Urinary retention with venlafaxine-fluoxetine combination

I would like to describe a patient showing urinary retention during treatment of depression with the combination of fluoxetine and venlafaxine. As both antidepressants have minimal anticholinergic effects, this seems an unusual case. A MEDLINE search did not find similar reports.

A 61-year-old man with a DSM-IV major depressive disorder had had a partial response to a 2-month trial of fluoxetine, 20 mg/day, without side effects. For this reason nortriptyline, 25 mg/day, was added to fluoxetine. Some days later he noted the appearance of moderate urinary difficulties. Two weeks later, this problem persisting, nortriptyline was discontinued, and urinary difficulties disappeared in a few days. As his depression was still present, venlafaxine, 37.5 mg/day, was added to fluoxetine to augment its antidepressant action. Two days later he noted the appearance of severe urinary difficulties (extreme difficulty to urinate). No other anticholinergic side effects were noted (no blurred vision, no constipation, no dry mouth, no tachycardia). Despite this relevant problem, he continued to take venlafaxine because his depression was improving. However, ten days later he discontinued venlafaxine because he could no longer tolerate these severe urinary difficulties. Two days later he noted the disappearance of all urinary problems.

He had a mild prostatic enlargement (confirmed by ultrasonography) which, in the past, had caused mild and sporadic urinary difficulties, but never the important urinary problems he had with nortriptyline and venlafaxine.

The appearance of urinary anticholinergic effects soon after venlafaxine intake, and their disappearance soon after venlafaxine discontinuation, suggest a causal link. A sudden, spontaneous, marked worsening, and a subsequent rapid improvement of his prostatic enlargement (on two occasions) seems unlikely.

As fluoxetine and venlafaxine are reported to have minimal or no anticholinergic effects (Baldessarini, 1996; Richelson, 1994), the typically anticholinergic urinary problems this patient had while taking these two drugs in combination needs an explanation.

Fluoxetine is a potent metabolic inhibitor of liver P450 cytochrome CYP2D6, which metabolizes venlafaxine (Ereshefsky *et al.*, 1997; Ereshefsky, 1996). Fluoxetine might have caused a marked increase of venlafaxine plasma level by inhibiting its metabolism, leading to a marked increase of its usually minimal anticholinergic effects. Their rapid disappearance after venlafaxine discontinuation is related to its short half-life (5–11 h, including its active metabolite O-desmethylvenlafaxine) (Ereshefsky *et al.*, 1997). Because this patient had a prostatic enlargement, he was particularly sensitive to the anticholinergic effects of medications at this site (he also had urinary problems with nortriptyline). That he did not report other anticholinergic side effects suggests that the absolute increase of the anticholinergic effects of venlafaxine was small. However, even a modest increase of venlafaxine anticholinergic effects might have been enough to cause severe urinary difficulties in this patient, because of his increased sensitivity to these effects at this site.

Another cause of his urinary difficulties might be serotonin effects on the bladder. Serotonin might inhibit micturition, and this effect may increase with age (Klarskov and Horby-Petersen, 1986; Espey and Downie, 1995; Saito *et al.*, 1993). Duloxetine, a serotonin and norepinephrine reuptake inhibitor like velafaxine, may suppress bladder activity through serotonin receptor mechanisms (Thor and Katofiasc, 1995). Its effects on bladder may be due to central mechanisms. The combined venlafaxine-fluoxetine inhibition of serotonin reuptake might have increased serotonin levels to the point of inhibiting micturition, with age and prostatic pathology as predisposing factors.

This case report suggests that the combination of venlafaxine with fluoxetine may cause severe urinary difficulties in individuals with even mild

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prostatic enlargement. A recent series of case reports (Benazzi, 1997a, b, c, d, e) suggest that the pharmacodynamics and pharmacokinetics of venlafaxine are more complex than reported up to now (Ereshefsky, 1996; Nemeroff *et al*., 1996).

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REFERENCES

Baldessarini, R. J. (1996). Drugs and the treatment of psychiatric disorders. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, Hardman, J. G., Limbird, L. E., Molinoff, P. B., Ruddon, R. W., Goodman Gilman, A. (Eds), McGraw-Hill, New York, p. 435.

Benazzi, F. (1997a). Urinary retention with venlafaxine-haloperidol combination. *Pharmacopsychiatry*, **30**, 27.

Benazzi, F. (1997b). Venlafaxine-clomipramine combination. *European Psychiatry*, **12**, 265–266.

Benazzi, F. (1997c). Venlafaxine-fluoxetine-nortriptyline interaction. *Journal of Psychiatry and Neuroscience*, **22**, 278–279.

Benazzi, F. (1997d). Anticholinergic toxic syndrome with venlafaxine-desipramine combination. *Pharmacopsychiatry*, in press.

Benazzi, F. (1997e). Severe anticholinergic side effects with venlafaxine-fluoxetine combination. *Canadian Journal of Psychiatry*, (in press).

Ereshefsky, L. (1996). Drug-drug interactions involving antidepressants: focus on venlafaxine. *Journal of Clinical Psychopharmacology*, **16** (Suppl. 2), 37S-53S.

Ereshefsky, L., Alfaro, C. L. and Lam, Y. W. F. (1997). Treating depression: potential drug interactions. *Psychiatric Annals*, **27**, 244–258.

Espey, M. J. and Downie, J. W. (1995). Serotonergic modulation of cat bladder function before and after spinal transection. *European Journal of Pharmacology*, **287**, 173–177.

Klarskov, P. and Horby-Petersen, J. (1986). Influence of serotonin on lower urinary tract smooth muscle in vitro. *British Journal of Urology*, **58**, 507–513.

Nemeroff, C. B., Lindsay De Vane, C. and Pollock, B. C. (1996). Newer antidepressants and the cytochrome P450 system. *American Journal of Psychiatry*, **153**, 311–320.

Richelson, E. (1994). The pharmacology of antidepressants at the synapse: focus on newer compounds. *Journal of Clinical Psychiatry*, **55** (Suppl. A), 34–39.

Saito, M., Kondo, A., Gotoh, M. Kato, K. and Levin, R. M. (1993). Age-related changes in the response of the rat urinary bladder to neurotransmitters. *Neurourology Urodynamics*, **12**, 191–200.

Thor, K. B. and Katofiasc, M. A. (1995). 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. *Journal of Pharmacology and Experimental Therapeutics*, **274**, 1014–1024.