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LETTER TO THE EDITOR

The Tyramine Pressor Test May Have Limited Sensitivity, Especially in the Presence of Dual Serotonin/Norepinephrine Uptake Inhibition☆

Turcotte and colleagues (2001) recently reported that duloxetine at oral doses up to 60 mg/day failed to blunt the pressor response to intravenous tyramine. However, recent data suggests that the tyramine pressor test results may be significantly confounded by several not yet understood factors. Prominent among these factors is the influence of concomitant serotonergic drug action. For example, venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI), also has a reduced effect on the tyramine challenge at the same doses that indicate physiologic norepinephrine activity (i.e., significant increase of blood pressure and heart rate) (Harvey et al. 2000). Additional confounding influences on the tyramine challenge include the duration of treatment prior to challenge and potential physiologic differences between normal and depressed subjects (Debonnel, et al. 1998; Harvey, et al. 2000).

Duloxetine demonstrates potent inhibition of both serotonin and norepinephrine uptake, with similar affinities, in several preparations including cloned human receptors (Bymaster et al. 2001). Duloxetine also produces simultaneous increases in extracellular serotonin and norepinephrine in rat hypothalamus and frontal cortex (Wong et al. 2000). Duloxetine at 80–120 mg/day in humans produces a reduction of urinary norepinephrine and its metabolites similar in magnitude to desipramine 100 mg (Chalon et al. 2000). At these doses, duloxetine also produces hemodynamic effects consistent with norepinephrine reuptake inhibition (Demitrack 2001; Goldstein et al. 2001; Turcotte et al. 2001). Finally, at doses of 40–120 mg/day, duloxetine produces a pattern of other clinical effects (e.g., dry mouth, sweating) consistent with enhancement of noradrenergic tone (Goldstein et al. 2001). The preponderance of evidence (receptor binding affinities, microdialysis, in vivo metabolite turnover, vital sign changes, and clinical effect data) clearly indicates that duloxetine produces norepinephrine uptake inhibition.

This evidence indicates that the tyramine pressor test may be inadequate to assess norepinephrine reuptake inhibition, especially in the presence of concomitant serotonin reuptake inhibition. In addition, the preponderance of evidence indicates that duloxetine has a pharmacological profile of potent and relatively balanced serotonin and norepinephrine reuptake inhibition.

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