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Duloxetine Pharmacology: Profile of a Dual Monoamine Modulator

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ABSTRACT

Dysregulation within central monoaminergic systems is believed to underlie the pathology of depression. Drugs that selectively inhibit the reuptake of central monoamines have been used clinically to alleviate symptoms of depressive illnesses. Duloxetine, a novel compound currently under investigation for the treatment of depression, binds selectively with high affinity to both norepinephrine (NE) and serotonin (5-HT) transporters and lacks affinity for monoamine receptors within the central nervous system. It has been suggested that dual inhibition of monoamine reuptake processes may offer advantages over other antidepressants currently in use.

In preclinical studies, duloxetine mimics many physiologic effects of antidepressants. Consistent with other antidepressants, duloxetine, by acute administration, elevates extracellular monoamine levels, while by chronic administration it does not alter basal monoamine levels. Like the selective serotonin reuptake inhibitor, fluoxetine, by microiontophoretic application, duloxetine inhibits neuronal cell firing. However, in comparison with fluoxetine, duloxetine is a more potent serotonin reuptake inhibitor. Furthermore, in behavioral experiments, duloxetine attenuates immobility in forced swim tests in animal models of depression to a greater extent than several other commonly used antidepressants.

In a six-week open label uncontrolled study, duloxetine was evaluated in patients with a history of depression. Duloxetine was effective in treating depression as determined by marked reduction in Hamilton Depression Rating scores. Adverse effects reported during duloxetine treatment were minor and similar to those of other antidepressants. In an eight-week multicenter, double-blind, placebo-controlled study in patients with a major depressive disorder, duloxetine was effective as an antidepressant, particularly in patients with greater symptom severity. Only limited data are available regarding the pharmacokinetic profile of duloxetine in humans, although a half-life of 10 to 15 h has been reported. Studies conducted in healthy human subjects confirm the preclinical profile of duloxetine as an inhibitor of 5-HT and NE reuptake. Taken together, existing data suggest that duloxetine is a novel and effective antidepressant.