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Alcohol and cocaine use disorders (AUD/CUD) are highly prevalent and difficult to treat. Behavioral and biological response to stress are largely attributed to neural processing in limbic, neocortical and brainstem structures. Although preclinical evidence supports anxiolytic effects of selective serotonin reuptake inhibitors (SSRIs) and some evidence for anxiogenic effects of certain antidepressants, the evidence is mixed and the impact of antidepressants on the stress response is a clinically relevant issue. The aim of the proposed study is to investigate the effects of duloxetine, one of the new generation antidepressants, on different elements of the stress response system including limbic, hypothalamic-pituitary-adrenal (HPA) and sympathoadrenal (SAD) responses to acute psychological stressors (trauma and stress). The blood concentration of duloxetine increases rapidly following a single dose of 60mg. Duloxetine's plasma concentration peaks after 3 hours and slowly declines over a 24-hour period. Duloxetine has also been shown to have a potent inhibitory effect of sympathetic outflow to the heart, which accounts for some of its antidepressant efficacy. The potential for stress-buffering effects of duloxetine may be attributable to its direct inhibitory effect on noradrenergic input to central catecholaminergic systems as well as its modulation of HPA and SAD responses. The specific aims of the proposed study are: 1) To determine effects of duloxetine on stress-evoked plasma concentrations of the stress hormones epinephrine and norepinephrine; 2) To determine the effect of duloxetine on the physiological stress responses to an acute psychological stressor - the Trier Social Stress Test; 3) To determine duloxetine's effects on the regulation of the pituitary-adrenal axis and on HPA and SAD activity as assessed by peripheral cortisol measurements and the secretion of ACTH and plasma norepinephrine; 4) To determine duloxetine's effects on cerebral blood flow response to stress. The aim of the proposed study is to examine the effects of duloxetine on different elements of the stress response system including limbic, hypothalamic-pituitary-adrenal (HPA) and sympathoadrenal (SAD) responses to acute psychological stressors. The results will assist in assessing whether duloxetine has important neuroendocrine correlates and whether it

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