of patients dropped out; only 8.5% because of adverse events and 0.7% due to lack of efficacy. Depressed mood as assessed on the CGI was very much or much improved at endpoint in 84.6% of patients. Mean score of severity of illness was significantly reduced from day 7 onwards (p < 0.0001). Adverse events reported with an incidence higher than or equal to 5% were somnolence (28.3%), weight increase (6.0%) and dry mouth (5.2%). Patients without sleep disturbances increased from 15.4% at baseline to 90% at study-endpoint. The number of patients with sexual dysfunction decreased from 69.2% at baseline to 25.9% after 6 weeks of treatment. The improvement was highly significant (p < 0.0001) on each factor of sexual functioning: drive, arousal, lubrication/erection, orgasm and satisfaction with orgasm.

Conclusions: Mirtazapine is an effective and well-tolerated antidepressant with additional beneficial effects on sleep improvement and sexual functioning.

**P03.272** THE ACUTE EFFECTS OF A SEROTONIN VERSUS A SEROTONIN AND NORADRENERGIC REUPTAKE INHIBITOR ON COGNITIVE AND PSYCHOMOTOR PERFORMANCE

P.J. Nathan, G. Sitaram, C. Stough, A. Sali, R.B. Silberstein. Brain Sciences Institute, Swinburne University of Technology, Melbourne, Australia

Currently several classes of antidepressants, tricyclics (TCAs), selective serotonergic reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs) are available for the treatment of clinical depression. Previous studies have suggested that the older generation antidepressant drugs may induce cognitive and psychomotor impairments while the newer antidepressants such as SSRIs and SNRIs are relatively free from cognitive psychomotor effects. However, more recent studies have shown that even with newer antidepressants positive or negative psychomotor and cognitive effects may be observed depending on the pharmacological selectivity and potency of the antidepressant. Comparisons of the behavioural side-effect profiles of antidepressants that selectively inhibit either serotonin (SHT) alone or both SHT and noradrenaline (NA) reuptake (TCAs and SNRIs), may reveal differences in cognitive and psychomotor functions, which may be attributed to their relative pharmacological selectivity for increasing monoamine concentrations in the brain. While previous studies have consistently investigated arousal and psychomotor effects, these studies have failed to investigate other cognitive processes such as working memory, sustained attention, visual scanning, information-processing speed or discriminative judgement abilities which may be modulated by both the serotonergic and noradrenergic systems. The aim of the present study was to determine the pharmacodynamic effects of clinical doses of citalopram and venlafaxine, a SSRI and SNRI class of antidepressants respectively, on a broader range of cognitive, psychomotor performance and subjective assessments of mood and well being. A positive (amitriptyline) control was employed to investigate the sensitivity of the psychometric tests to drug-induced change. Nine healthy male volunteers (mean age 25.3 years, mean weight 74.1 kg) received a single dose of citalopram (20 mg), venlafaxine (37.5 mg), or amitriptyline (25 mg) in a placebo controlled double blind design. Subjects were administered a battery of cognitive and psychomotor tests (critical flicker fusion, choice reaction time, digit span test, digit symbol substitution, inspection time, trail making test) and a subjective measure of sedation (line analogue scale), pre and post 1, 2 and 4 hours post administration. The positive control amitriptyline impaired performances on majority cognitive and psychomotor tests. Compared to placebo, Citalopram improved psychomotor responses to sensory stimuli and sustained attention, with significant decreases in movement times of the Choice Reaction Time test (F = 11.57, p < 0.05), and an increase in Critical Flicker Fusion threshold (F = 11.44, p < 0.01). Venlafaxine on the hand did not improve performances on psychomotor responses to sensory stimuli, sustained attention, information processing, working memory and did not increase arousal. Furthermore no differences were found between Citalopram and Venlafaxine in all cognitive and psychomotor tests investigated. It was concluded, that the behavioural side-effects associated with the dual reuptake inhibitory actions on serotonergic and noradrenergic systems, after acute administration of venlafaxine, were not significantly different from those associated with the selective reuptake inhibitory actions on the serotonergic system after acute administration of citalopram.

**P03.273** FLUOXETINE INCREASES INTRACELLULAR Ca2+ CONCENTRATIONS IN MADIN-DARBY CANINE KIDNEY CELLS

K.Y. Tang, S.P. Wang, C.R. Jan. Kaohsiung Veterans General Hospital, Psychiatry, Kaohsiung, Taiwan, China

**Rational:** The effect of fluoxetine on cellular Ca2+ signaling is unclear.

**Objectives:** To explore the effect of fluoxetine on intracellular free Ca2+ concentrations ([Ca2+]i) in intact cells.

**Methods:** The effect of fluoxetine on Ca2+ signaling in populations of Madin-Darby canine kidney (MDCK) cells was investigated by using fura-2 as a Ca2+ probe.

**Results:** Fluoxetine increased [Ca2+]i concentration-dependently between 0.250 µM and 200 µM. The response was partly inhibited by external Ca2+ removal. In Ca2+-free medium pretreatment with 1 mM thapsigargin, an inhibitor of the endoplasmic reticulum Ca2+ pump, abolished 100 µM fluoxetine-induced Ca2+ release. Addition of 3 mM Ca2+ increased [Ca2+]i after pretreatment with 100 µM fluoxetine in Ca2+-free medium. Suppression of 1,4,5-trisphosphate (IP3) formation by 2 mM U73122 (a phospholipase C inhibitor) did not affect 100 µM fluoxetine-induced Ca2+ release. Fluoxetine (5–100 µM) also increased [Ca2+]i in human neutrophils, prostate cancer and bladder cancer cells, and rat glroma cells.

**Conclusions:** Fluoxetine increased [Ca2+]i in MDCK cells, concentration-dependently, by releasing Ca2+ from thapsigargin-sensitive Ca2+ stores in an IP3-independent manner, followed by Ca2+ influx from external space.

**P03.274** BUPROPION SR FOR SSRI-RESISTANT MAJOR DEPRESSION

P.J. McGlashan1, D. Fava1, J.W. Stewart1, F.M. Quitkin1, J.E. Alpert2, A. Nierenberg2.1 New York State Psychiatric Institute & Columbia University College of Physicians & Surgeons; 2Massachusetts General Hospital & Harvard Medical School, Boston, Massachusetts, USA

Many patients with Major Depression fail to respond to an SSRI trial, making this a common and significant clinical problem. For these patients, treatment with a medication like sustained-release bupropion (Wellbutrin SR), thought to act by noradrenergic and possibly dopaminergic mechanisms, may be a more rational strategy than switching to another SSRI. We report preliminary results for the first 18 such subjects from a clinical trial who failed to respond to fluoxetine (>40 mg for ≥8 weeks) and were switched to bupropion SR 150 mg, twice daily without washout. Thirteen subjects (72%) completed the trial. Responders were considered those with a ≥50% decrease in baseline HAM-D on screening at endpoint, partial responders those with ≤50% but ≥25% decrease, and nonresponders those with ≤25% decrease.

Of 18 patients, 5 (28%) were considered responders, 5 (28%) partial responders, 8 (44%) nonresponders. While no evidence of major adverse interaction with remaining fluoxetine and norfluoxetine was found, our small sample size precludes finding any but a large effect. These data suggest that bupropion SR treatment is well tolerated in fluoxetine nonresponders without a washout and may be effective for SSRI nonresponders.

Funding was provided by GlaxoWellcome Inc., NIMH R01 MH 56058, and the Office of Mental Health of the State of New York.


**P03.275** REBOXEPINE HAS IMMUNE-ENHANCING PROPERTIES IN MAJOR DEPRESSION: A PILOT STUDY

C. Reynaert1, P. Jann1, A. Pauwels, N. Zdanowicz1, Ph. Satquet1, B. Chatelain1, W. Stekkel1.1 Université Catholique de Louvain, Cliniques Universitaires de Mont-Godinne, Yvoir; 2Pharmacia Upjohn Belgium, Brussels, Belgium

**Objective:** Depressed mood has been associated with reduced natural killer cell activity (NKCA). The aim of this study was to assess the reversibility – under a 21 day treatment with reboxetine – of this NKCA defect observed at baseline in depressed patients by comparing them to a healthy control group.

**Methods:** We evaluated NKCA (in vitro) before and during treatment with the noradrenaline reuptake inhibitor (NARI) reboxetine (Edronax® 8 mg/day) within a 21 days comparative pilot study design. K562 cells incubated with 0.2 mCi 51Cr (sodium chromate) were used as target cells. Peripheral blood lymphocytes were added as effectors cells at various effector:target ratios. 14 patients with major depression, according the DSM IV criteria, were treated with reboxetine and compared to 14 untreated sex, age, tobacco, alcohol and caffeine use-matched healthy control subjects. HAM-D, MADRS, CGI and NKCA were