Results: This selectivity is the result of a more potent blockade of serotonin 5HT2 receptors than dopamine D2 receptors. However, this property is also shared by most other atypical antipsychotic agents and would not alone explain quetiapine's placebo levels of extrapyramidal symptoms and prolactin levels compared to other atypical agents. Recent findings suggest another property of quetiapine that may better explain its clozapine-like profile on extrapyramidal symptoms and prolactin. Quetiapine appears to bind loosely to the striatal D2 dopamine receptor and is readily displaced by dopamine. The rapid release of quetiapine from the D2 receptor may contribute to the transient occupancy of striatal D2 receptors observed in schizophrenic patients treated with therapeutic doses of quetiapine. Thus, quetiapine may be acting in a modulatory manner at the D2 receptor, permitting dopamine to achieve a more normal physiologic role at the same receptor.

Conclusions: These observations support the concept that quetiapine is acting in a fundamentally different manner than other antipsychotic drugs, and may be the mechanism underpinning quetiapine's clozapine-like preclinical profile as well as its proven clinical effectiveness in treating symptoms of schizophrenia without producing extrapyramidal symptoms and endocrine (prolactin-related) abnormalities.

577. VALPROATE INHIBITS OXIDATIVE STRESS IN PRIMARY CULTURED RAT CEREBRAL CORTICAL CELLS

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Background: Previous studies showed that chronic valproate treatment increased the expression of the molecular chaperones GRP78 and GRP94, and the anti-apoptotic factor bcl-2, which all have cytoprotective effects. To further characterize these neuroprotective effects, we studied the effect of valproate on oxidative stress induced cell damage.

Methods: Malondialdehyde (MDA), an end product derived from peroxidation of polyunsaturated fatty acid, and protein carbonyls were used to assess oxidative damage to lipid and protein. Northern blotting and immunoblotting analysis were used to measure mRNA and protein levels of glutathione S-transferase (GST). GST activity was analyzed using CNDB as a substrate.

Results: In primary cultured rat cerebral cortical cells, we found that although chronic treatment with valproate at concentrations of 0.15-1.2 mM for one week had no effect on MDA accumulation, chronic treatment with this drug at both 0.6 and 1.2 mM significantly reduced MDA accumulation induced by oxidant FeCl3. In addition, chronic treatment with valproate at 0.6 and 1.2 mM significantly inhibited protein oxidation induced by FeCl3. Glutathione S-transferase conjugates the reduced glutathione thiolate anion with a variety of electrophiles including oxidized lipid and DNA to play an important role in cellular protection against oxidative stress. We found that chronic treatment with valproate increased mRNA and protein levels of this enzyme. Valproate also increased GST activity in dose- and time- dependent fashion.

Conclusions: Our results suggest that chronic valproate treatment protects neuronal cells from damage caused by oxidative stress, and that neuroprotection from oxidative damages may be involved in the mechanism of action of this drug.

578. NO LASTING EFFECTS OF MODERATE DOSES OF MDMA (ECSTASY) ON MEMORY PERFORMANCE AND MOOD STATES IN HEALTHY HUMANS

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Background: Impaired cognitive performance and an increase of anxiety and depression has been reported following ecstasy use. The purpose of this study was to investigate whether memory functions as well as anxious and depressive mood states were affected by administration of two doses of MDMA in healthy humans for a period of fourteen days.

Methods: Using the CANTAB battery and psychological ratings, fifteen MDMA-naive subjects were examined on visual and working memory performance and affects two weeks before and after the administration of two moderate doses of MDMA (1.6 mg/kg p.o.) given two weeks apart. The effects of MDMA on memory functions and mood states were analyzed using a repeated measure two-way ANOVA and Effect Sizes according to Cohen's method.

Results: Healthy MDMA naive humans performed similarly on visual and working memory tests and showed no significant alterations in anxious and depressive mood states two weeks before and following the administration of MDMA.

Conclusions: These results supports the hypothesis that two moderate doses of MDMA do not alter significantly visual and working memory performance as well as anxious and depressive mood states in healthy volunteers.

579. DIFFERENCES BETWEEN PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS FOR METHYLPHENIDATE AND ATOMOXETINE

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Background: Methylphenidate (MPH) is an approved dopaminergic drug to treat attention-deficit/hyperactivity disorder (ADHD). Atomoxetine (ATMX) is an investigational drug for treatment of ADHD that is a highly selective norepinephrine reuptake inhibitor. Because of different mechanisms-of-action (MOA), this study examines the relationship between pharmacokinetic/pharmacodynamic (PK/PD) relationships for MPH and ATMX.

Methods: The PK/PD relationships for MPH in a lab school study were obtained from published literature (Clin Pharmacol Ther 1999, 66:295–305). The PK/PD relationship for ATMX was determined in a large, multi-site, fixed-dose, double-blind, placebo-controlled trial in children and adolescents with twice-daily dosing.

Results: MPH demonstrated complex PK/PD relationships. Despite similar area-under-the-curves (AUCs), different dosing patterns resulted in different patterns of reductions in ADHD symptoms, partly due to tachyphylaxis. The PK/PD relationship for ATMX is characterized by an E_{max} model describing reduction in ADHD symptoms with increasing AUC.

Conclusions: Consistent with different MOAs, PK/PD relationships appear different for MPH and ATMX. The ATMX PK/PD relationship predicts similar reductions in ADHD symptoms will result when ATMX is administered once daily or as a divided twice-daily dose since the same AUC_{0-24} would result in both cases. Additional research is needed (to