

this approach, we have recently identified the histamine H1-receptor as a likely proximal molecular target for atypical antipsychotic drug-induced weight gain (Kroeze et al, *Neuropsychopharmacol*, in press) and are currently using datamining technologies to discover sites responsible for other actions of atypical antipsychotic drugs. We have also recently discovered that the kappa opioid receptor represents a potential target for antipsychotic drug development based on the preferential actions of a novel hallucinogen at this site (Roth et al, *PNAS*, in press). It is likely that this massively parallel approach will allow for the discovery of additional novel molecular targets for antipsychotic drug actions and will clarify the targets responsible for serious side-effects associated with antipsychotic drug treatment.

### THE RELATIONSHIP OF ESTROGEN AND CORTISOL TO PREPULSE INHIBITION OF THE ACOUSTIC STARTLE IN SCHIZOPHRENIA

T. Sharma,\* V. Kumari

*Clinical Neuroscience Research Centre, Dartford, Kent, United Kingdom*

Prepulse inhibition (PPI) of the startle response refers to a reduction in the response to a startling stimulus (pulse) if it is preceded briefly (30-500 ms) by a weak pre-stimulus (prepulse). PPI is found to be reduced in schizophrenia. Epidemiological evidence suggests gender differences in age at onset and symptoms of schizophrenia. Recently estrogen has been shown to enhance PPI of the acoustic startle in the rat (1). We, therefore, investigated the association between basal levels of estrogen to PPI in schizophrenia. In addition, we also examined the relationship between cortisol levels and PPI in this sample. The study involved 30 patients (20 men, 10 women) with schizophrenia, all medicated with conventional antipsychotics, who were tested identically on a single occasion for PPI of the acoustic startle response. Prepulse stimuli (14 dB above the background) preceded the pulse stimuli with prepulse onset to pulse onset intervals of 30, 60, 90, 120, 150 or 1000 milliseconds. They also provided blood samples which were analyzed for concentrations of estradiol and cortisol. The results revealed trends for positive association between estradiol levels and PPI (most strong relationship with PPI produced by 60-ms prepulse-to-pulse interval trials). Estradiol levels had no relationship with amplitude over the pulse-alone trials. Cortisol was weakly (mostly non-significantly) negatively correlated with PPI levels. High levels of estradiol also predicted low symptom scores. Our findings suggest that treatment with estrogen may have beneficial effects on symptoms and sensorimotor gating deficits, as assessed with prepulse paradigms, in schizophrenia. (1) Van den Buuse M, Eikelis N (2001) Estrogen increases prepulse inhibition of acoustic startle in rats. *Eur J Pharmacol* 425(1):33-41 Acknowledgement: VK holds a Beit Memorial Foundation Research Fellowship.

### USE OF HIGHER-DOSE QUETIAPINE IN ELDERLY INPATIENTS: A CHART REVIEW STUDY

F. Sicuro

*Long Term Psychiatric Management, PC, St. Louis, MO, USA*

Objective: To identify elderly patients who were treated with doses of 200-mg quetiapine or greater to evaluate both efficacy and safety parameters. Methods: Charts were reviewed at a single geropsychiatric inpatient unit over a course of 15 months to identify patients taking quetiapine. 91 patients were identified (age range 32-102 y, mean age 68 y). 28 patients were analyzed (aged 65 y or older and taking at least 200 mg of quetiapine). Results: Mean age was 78.5

years. 20 patients (71%) were female. Most common reason for admission was agitation and/or aggression. Most common primary diagnoses were dementia with psychosis (82%) and dementia complicated by depression (50%). Mean quetiapine dosage on discharge was 450 mg/d, and average dosage increase during admission was 262 mg/d. Of patients newly started on quetiapine, 10/12 (83%) reached 200 mg within 4 days. Patients with comorbid depression required 49% higher dosage of quetiapine than those without depression (539 mg/d vs 361 mg/d, respectively). Mean improvement in CGI scores was 56.5% (from moderately-markedly ill to much improved). 9 patients experienced a fall during the course of hospitalization (total of 18 episodes); 11 episodes were due to as-needed medications (haloperidol, lorazepam, or fluphenazine), 5 episodes occurred while the patient was taking quetiapine and a second neuroleptic, and 2 episodes occurred while the patient was not taking quetiapine. No patients reported falling while on quetiapine alone. Quetiapine doses for patients experiencing no falls throughout admission were higher than doses used in patients who experienced a fall (482 mg/d vs 378 mg/d, respectively). 5 patients (18%) experienced sedation unexplained by doses of as-needed medication. 3 of 5 cases were temporally related to initial titration phase of quetiapine. Mean discharge dose for quetiapine was higher in the group experiencing no sedation or sedation due to as-needed medications compared with the group experiencing sedation unrelated to as-needed medication (464 mg/d vs 385 mg/d). 2 patients (7%) developed EPS while taking quetiapine; however, both patients were also receiving routine dosages of haloperidol. Conclusions: This is the first report of the use of quetiapine in dosages above 200 mg/d in the elderly population. We found quetiapine to be very effective and safe in treating elderly demented patients with psychosis and agitation in an inpatient setting. Additional, prospective studies are needed.

### COGNITIVE ENHANCEMENT TRIAL WITH GUANFACINE IN SPD

L. J. Siever,\* P. Harvey, D. Barch, V. Mitropoulou, M. Goodman, H. W. Koenigsberg

*Psychiatry, Mt. Sinai School of Medicine, New York, NY, USA*

$\alpha$ -adrenergic antagonism has been demonstrated to play an important role in working memory in animal studies and in clinical studies in Attention Deficit Disorder with Hyperactivity, Korsakoff's Syndrome and in one pilot study in schizophrenia. Working memory and attentional impairment in schizotypal personality disorder (SPD) are similar in character to those observed in schizophrenia but less severe and more easily reversible. For these reasons, a trial of guanfacine to assess its effects on cognitive function, specifically working memory and attention, was initiated in patients with SPD. **Method:** Nine patients received active guanfacine in a dose up to 2 mg per day while four subjects have received placebo in a "staggered start" protocol of eight weeks. Subjects were administered tests of working memory including the Paced Auditory Serial Addition Test (PASAT), N-back Continuous Performance Test (CPT) and the modified AX-CPT before and following treatment in an ongoing pharmacologic trial. Five of the six patients with baseline impairment on the PASAT tended to improve on guanfacine, while none changed on placebo on the modified AX-CPT Fisher's Exact ( $p=0.1$ ). A similar proportion of patients improved on the N-back test with guanfacine. Guanfacine reduced the number of BX errors while it increased the number of AY errors especially in the interference and degraded stimulus versions of this CPT resulting in a statistically significant drug effect across these tasks ( $p<0.01$ ). While results are preliminary, effect sizes were generally greater than those observed in studies of

cognitive function in schizophrenic patients treated with atypical antipsychotic medications. **Discussion:** These results of our pilot sample, which will be updated at the meeting, raised the possibility that guanfacine may enhance working memory and attentional performance in SPD patients and may provide a promising tool to understand the pharmacologic underpinnings of the cognitive deficits of the schizophrenia spectrum disorders.

### EFFECTS OF SMOKING AND NICOTINE NASAL SPRAY ON COGNITION AND AFFECT IN SCHIZOPHRENIA

R. C. Smith,\* A. Singh, A. Khandat, M. Infante, J. Warner-Cohen

*Psychiatry, NYU Medical School, New York, NY, USA*

Schizophrenics having among the highest rates of cigarette smoking of any diagnostic group. Studies by other groups have that suggested abnormalities in psychophysiological responses, putatively related to information processing, are transiently ameliorated by smoking; they have also reported allelic abnormalities in the  $\alpha$ -7 nicotinic receptor in schizophrenic patients which may be related to the illness and differential effects of cigarettes or nicotine in schizophrenic patients. There has been less experimental work to see whether smoking or nicotine ameliorates the cognitive and negative symptom deficits in schizophrenia which have been hypothesized as additional mediating factors underlying the high rates of smoking in schizophrenic patients. We have been conducting a series of experimental studies on the effects of smoking cigarettes and nicotine nasal spray on cognitive and affective functioning in schizophrenic patients using double-blind placebo-controlled designs. The results of our experiments show that: 1) high dose nicotine cigarettes significantly decrease interview rated negative symptoms more than placebo (minimal-dose nicotine) cigarettes, but nicotine nasal spray had no effects on negative symptoms; 2) Active nicotine nasal spray, compared to placebo, significantly improved performance on cognitive tasks involving spatial rotation and two-choice reaction time, and high dose cigarettes showed a significant effect on these measures compared to same day pre-drug measures. However, tolerance effects may influence the strength or interpretation of the cognitive test results. Preliminary results from additional studies, in progress, to address this problem, suggest that nicotine nasal spray improves attentional performance in schizophrenics on some measures of the CPT. There are trends for a differential effects of active vs. placebo nicotine spray on digit span and visual spatial memory. These results of our studies support the contention that smoking or nicotine may improve cognitive and affective deficits in schizophrenic patients. It is possible that these effects are related to nicotinic receptor abnormalities in schizophrenia and/or the high rate of smoking in patients with this disorder.

### EFFECT OF THE SELECTIVE DOPAMINE D3 RECEPTOR ANTAGONIST SB-277011 ON REGIONAL FOS EXPRESSION IN THE RAT FOREBRAIN

E. Southam,\* C. A. Jennings, J. E. Cluderay, J. Gartlon, J. Cilia, D. N. Jones

*Psychiatry Centre of Excellence for Drug Discovery, GlaxoSmithKline, Harlow, Essex, United Kingdom*

SB-277011 is a high affinity and selective antagonist of human and rat dopamine D3 receptors with a preclinical profile suggestive of an

antipsychotic agent (Reavill, C. et al., 2000, JPET, 294:1154-1165). Immediate early gene expression is a well established marker of neuronal activation resulting from a variety of stimuli including typical and atypical antipsychotic drugs. To characterise further the pre-clinical properties of SB-277011, we have used Fos immunohistochemistry to probe the functional consequences of its action in the rat forebrain. Two, four, or six hours after the oral administration of SB-277011 (30 mg/kg) or vehicle, rats were perfused fixed with depolymerised 4 % paraformaldehyde and 50  $\mu$ m thick coronal fore-brain sections prepared using a cryostat. Fos protein was immunolabelled using a rabbit polyclonal antiserum and the density of positive cells within predefined areas assessed using an image analysis system. Compared with vehicle, SB-277011 significantly ( $p < 0.05$ ) increased the density of Fos-positive cells in both the core and shell of the nucleus accumbens and in the lateral septum (ventral). The response was time dependent with the greatest effect seen 2 hours post administration. No effect of SB-277011 on the density of Fos-positive cells was observed in the caudate nucleus (lateral or medial) or in the cingulate, infralimbic prefrontal, or somatosensory cortices. The regional pattern of increased Fos expression caused by SB-277011 mirrors the distribution of the D3 dopamine receptor in the rat forebrain and corresponds well with behavioural data. Increased Fos in the nucleus accumbens reflects the capacity of the compound to reverse deficits in prepulse inhibition seen in isolation reared rats whilst the absence of an increase in the caudate putamen reflects the low propensity of D3 receptor antagonists to cause motor side effects. These data add to a preclinical profile which is suggestive of an antipsychotic agent with a low propensity to cause motor side-effects.

### RNA EXPRESSION PROFILING REVEALS ALTERATIONS IN LIPID METABOLISM-RELATED MOLECULES IN RESPONSE TO ANTIPSYCHOTIC DRUG TREATMENT: INSIGHTS INTO THE PATHOPHYSIOLOGY OF PSYCHIATRIC DISORDERS

E. A. Thomas,\* A. J. Warren, D. Lo, J. G. Sutcliffe  
*Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA, USA*

Using an automated PCR-based genomics approach, TTotal Gene expression Analysis (TOGA), we've examined gene expression profiles of mouse striatum and cortex in response to clozapine and haloperidol drug treatment. Of approximately 11,000 mRNAs screened, several groups of related molecules were identified to be regulated by drug treatment. Genes involved in neurotransmission, signal transduction, oxidative stress, cell adhesion, apoptosis and proteolysis were altered in the brains of both clozapine- and haloperidol-treated mice. Highly notable was the differential expression of genes associated with lipid metabolism. These include apolipoprotein D (apoD), the mouse homolog of oxysterol binding protein-like 8 (OSBPL8) and the diacylglycerol receptor, n-chimaerin. Real-time PCR analysis confirmed increases in the expression of apoD (1.6 to 2.2-fold) and OSBPL8 (1.7 to 2.6-fold), and a decrease in the expression of n-chimaerin (1.5-2.2-fold), as well as changes in other molecules, in response to haloperidol and clozapine treatment. While antipsychotic drugs may be working to correct dysfunctions in several systems in psychiatric disorders, lipid metabolism/signaling pathways may be of particular importance in the mechanisms of