### S-20.004 Neuromodulation in impulsivity and prefrontal cortex

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**Objective:** Prefrontal cortex, particularly orbital frontal cortex, plays a modulatory role in regulating affective arousal and impulsive aggression through dampening amygdala activity. Neuromodulator systems such as the serotonin system and neuropeptides such as the opioids may modulate prefrontal activity gating inhibition of affective aggression. Orbital frontal cortex is modulated by serotonin via 5-HT2A receptors and by opioids through mu-opioid receptors. Polymorphisms in the 5-HT2A receptor, TPH2 receptor and mu-opioid receptor thus may regulate impulsive aggression. These genetic and imaging variables were thus investigated in this study.

**Methods:** In overlapping cohorts patients with personality disorder, largely BPD patients, and IED-IR (intermittent explosive disorder-integrated research), were imaged on a paradigm for basal activity and provocation of aggression in a FDG PET paradigm and 5-HT2A binding was evaluated in patients with current physical aggression. Polymorphisms of TPH2, 5-HT2A receptor, and mu-opioid receptor were evaluated in a larger cohort of patients.

**Results:** IED-IR patients demonstrate reduced basal prefrontal activity, increased amygdala activity, and orbital frontal compensatory activation on provocation of aggression. Increased 5-HT2A receptors are associated with current aggression and a 5-HT2A allele while polymorphisms in the TPH2 receptor, are associated with aggression and reduced prefrontal activation. The mu-opioid receptor allele is associated with affective instability and reduced prefrontal activation.

**Conclusion:** These data suggest that prefrontal cortex inefficiently regulates amygdala with impulsive aggressive. 5-HT2A receptors may be important in modulating this aggression and vary in a state-related manner depending on stress. Genetic variation and components of the serotonin system such as TPH2 and 5-HT2A appear to alter the degree of prefrontal activation and alleles of TPH2 and of the mu-opioid are associated with reduced prefrontal function and associated affective or impulsive behaviors. Thus, neuromodulators such as serotonin and opioids may set the gain in prefrontal inhibition of limbic structures and regulation of aggression.

**Policy of full disclosure:** None.

## S-36. Nicotine: Nicotine dependence and psychiatric comorbidity

### S-36.001 Smoking and schizophrenia. Basic mechanisms

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**Objective:** The heavy cigarette smoking in schizophrenia may reflect a reduced expression of a7* nicotinic acetylcholine receptors (a7*nAChRs) in several areas of the brain, which contributes to impairment of sensory gating and cognitive dysfunction. Since the high nicotine levels associated with heavy smoking may be needed to activate a7*nAChRs, which may rapidly desensitize, allosteric potentiators of these receptors might represent an interesting adjunctive treatment as indicated by some clinical results.

**Methods:** We used rats and single cell recording in vivo from dopamine (DA) neurons in the ventral tegmental area and microdialysis in awake freely moving animals to assess regional DA release in brain. Motor activity and conditioned avoidance response (CAR) was used to assess the antipsychotic potential of the drugs tested, i.e. galantamine, which in low doses is a positive allosteric modulator of nAChRs, binding to the a-subunit, and at higher doses is an ACh esterase inhibitor, and donepezil, an ACh esterase inhibitor without being an allosteric nAChR modulator.

**Results:** In contrast to donepezil, low doses of galantamine stimulated basal firing and burst activity in midbrain DA neurons, an effect antagonized by both the nAChR antagonist mecamylamine and by α7nAChR blockage, but not by scopolamine. Low doses of galantamine, but not donepezil, caused a preferential increase in prefrontal DA output in similarity with atypical, but not typical antipsychotic drugs as well as subchronic, intermittent nicotine administration. Galantamine, but not donepezil antagonized amphetamine-induced DA release in brain and potentiated the antipsychotic-like effect of the D2 antagonist raclopride in the CAR model.

**Conclusion:** These data propose that the antipsychotic-like effect of adjunctive galantamine may be related to allosteric modulation of a7*nAChRs. This is supported by the fact that its specific anti-psychotic-like effect could not be mimicked by the selective AChE inhibitor donepezil and, moreover, that the antipsychotic-like effect of galantamine was lost at higher dosage.

**Policy of full disclosure:** Johnson & Johnson, AstraZeneca, Schering-Plough, BiRDS Pharma GmbH.

### S-36.002 Nicotine impact on the dopamine system – relationship to the pathophysiology of depression

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**Objective:** Patients with depression exhibit an abnormal focus on internal state and rumination, which could be interpreted as a hypercontextual focusing of attention. Contextual focus is mediated by the ventral subiculum of the hippocampus, a region that receives potent drive from several stress-related regions including the amygdala. Repeated stress, such as that associated with models of depression, lead to abnormal potentiation of activity within the subiculum-ventral striatal pathway. We propose that pharmacological intervention that interrupts the abnormal ventral subiculum-ventral striatal drive can be an effective therapeutic intervention in depression.

**Methods:** Rats are subjected to repeated stress to induce learned helplessness model of depression. In vivo recordings are made from ventral subiculum neurons and of local field potentials in the ventral striatum of anesthetized rats, and theta burst stimulation applied to the subiculum.

**Results:** We found that repeated stress results in potentiation of synaptic drive in the ventral subiculum-ventral striatal pathway. Moreover, when this system is hyperactive it blunts the ability of the prefrontal cortex to allow behavioral flexibility. This subiculum-ventral striatal long-term potentiation is interrupted by systemic administration of ketamine or by high-frequency stimulation of the prefrontal cortex. Furthermore, interventions that potentiate interneuron activity within the subiculum can reverse hyperactivity within this region.

**Conclusion:** In depression, the patient is abnormally focused on their own state, which we propose is due to contextual inflexibility driven by hyperactivity within ventral subicular output pathways. In order to enable the patient to break out of this condition, the prefrontal cortex must gain control to allow shifting of attention from the internal ruminative state to focus on events in the environment. This can be achieved by attenuating activity within the subiculum-ventral striatal pathway. In particular, drugs such as nicotinic agonists or GABA modulators can act to augment interneuron control of the subiculum and restore balance to this system.

**Policy of full disclosure:** Johnson & Johnson, Taisho, Lundbeck, Abbott, Galaxo Smith Kline

### S-36.003 Molecular, behavioral and neural circuitry studies on varenicline: Implications for the mechanism of action of partial agonists

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**Objective:** The dual agonist and antagonist actions of the α4β2 nicotinic acetylcholine receptor (nAChR) partial agonist, varenicline, are key mechanisms underlying its clinical efficacy in smoking cessation. Further studies are have been conducted to advance our understanding of the mechanism of action of nAChR partial agonists on the molecular, behavioral and neural circuitry.

**Methods:** Three studies will be discussed: 1) Functional activities at major nAChR subtypes, measured by electrophysiology (Rollema et al., Brit J Pharmacol 2010); 2) Effects on reinstatement of nicotine self-administration, determined in a rat behavioural model (O'Connor et al., Psychopharmacology 2009); 3) Neuroimaging studies of the effect of varenicline on the brain 'at rest' and during smoking cue exposure (Franklin et al., ACNP, 2009).