of 100 mg (39%) or 125 mg (33%) was similar to that seen in KAR-001, our previous phase 1 study (34%). Most ChAEs occurred within the first few days of starting or increasing the study drug. The majority of these AEs at 100 mg and 125 mg xanomeline-dose levels were mild and transient in nature. None of the cohorts showed meaningful changes in orthostatic HR or obvious differences in BP between placebo and KarXT compared to placebo. All cohorts receiving KarXT showed placebo-adjusted increases in mean resting HR consistent with past studies with xanomeline where short-term increases in resting HR were observed that normalized to baseline over time. Both trospium and xanomeline exposures (AUCs) and variability were comparable to KAR-001 where the compounds were given using separate formulations.

**Discussion:** The new KarXT co-formulation of xanomeline and trospium performed well in healthy subjects and is currently being tested in patients with schizophrenia. Longer terms studies will provide further data around the safety and tolerability of KarXT, as well as the possible attenuation of AEs over time. Importantly, the tolerability observed in this healthy volunteer study may not be representative of schizophrenic patients, who tolerate currently marketed antipsychotic medicine better than healthy volunteers. No new safety signals were reported in the present study. The timing and duration of AEs were related to peak drug levels (C_max) and suggest that there is a potential for increased tolerability over time. In addition, all AEs rapidly returned to baseline levels upon dosing discontinuation. Consistent with our previous studies, KarXT is substantially better tolerated than xanomeline alone.

**T107. MEDICATION ADHERENCE USING ELECTRONIC MONITORING IN SEVERE PSYCHIATRIC ILLNESS: 4 AND 24 WEEKS AFTER DISCHARGE**

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**Background:** The purpose of this study was to examine post-hospitalization outpatient drug adherence in patients with severe psychiatric illness, including bipolar disorder and schizophrenia, and to investigate factors associated with drug adherence.

**Methods:** Eighty-one patients diagnosed with schizophrenia or bipolar disorder who were hospitalized due to aggravation of psychiatric symptoms such as the Clinical Global Impression-Severity, Drug Attitude Inventory, Multidimensional Scale of Perceived Social Support scale, and patients’ demographic factors. We measured drug adherence using the Medication Event Monitoring System (MEMS), pill count, and patients’ self-report upon out-patients visits, 4 and 24 weeks after discharge.

**Results:** The mean values of the various measures of adherence were as follows: MEMS (4 weeks) 84.81%, pill count (4 weeks) 94.6%, self-report (4 weeks) 92.6%, MEMS (24 weeks) 81.6%, pill count (24 weeks) 90.6%, self-report (24 weeks) 93.6%. The adherence agreement between MEMS, pill count, and self-report was moderate. (4 weeks intra-class correlation[ICC] = 0.54, 24 weeks ICC = 0.52) Non-adherence (MEMS<0.80) was observed in 26.4% of the patients at 4 weeks and 37.7% at 24 weeks. There was a negative correlation between drug adherence assessed 4 weeks after discharge and Contour Drawing Rating Scale difference score (r=0.282, p<0.05). A positive correlation was found between drug adherence assessed 24 weeks after discharge and Drug Attitude Inventory (r=0.383, p<0.01).

**Discussion:** Patients’ attitude towards their medication and their degree of physical dissatisfaction influenced post-hospitalization drug adherence in severe psychiatric patients with schizophrenia or bipolar disorder.

**T108. AUTO0206, A NOVEL KV3 CHANNEL MODULATOR, REDUCES KETAMINE-INDUCED BOLD SIGNAL IN HEALTHY MALE VOLUNTEERS: A RANDOMISED PLACEBO-CONTROLLED CROSSOVER TRIAL**

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**Background:** Evidence suggests that schizophrenia involves impaired functioning of fast spiking (FS) GABA interneurons and disinhibition of glutamate release. Acute ketamine disrupts interneuron-pyramidal neuron balance, increases network activity, and increases the cortical blood oxygen level dependent (BOLD) signal in magnetic resonance imaging (MRI) studies in rodents and humans. In humans, ketamine markedly increased BOLD signal in dorsal anterior cingulate (dACC) and in precuneus, which correlated with psychosis-like subjective effects of the drug. These effects were reduced by pre-treatment with lamotrigine (Deakin et al PMID:18250253).

AUTO0206 is a positive modulator of Kv3.1 and Kv3.2 channels that are located on fast-spiking cortical GABA interneurons. We have previously reported that AUTO0206 reduced the BOLD response to acute ketamine in rodents. The present study explored the effects of AUTO0206 in an acute ketamine challenge study in healthy volunteers.

**Methods:** The design was a single-centre, double-blind, placebo-controlled, crossover study for 16 healthy participants. AUTO0206 (800 mg, 2000 mg) or placebo was administered 4 hours prior to the intravenous infusion of ketamine or saline during MR BOLD imaging. Saline was infused for 8 minutes (baseline), followed by ketamine (bolus of 0.26 mg/kg for 1 min, maintenance of 0.25 mg/kg/h for 30 mins) or continued saline. The BOLD signal was followed for a further 16 mins. Participants attended 4 pharmaco-MRI sessions in which they received (in random order) placebo + saline, placebo + ketamine, 2000 mg AUTO0206 + ketamine, 800 mg AUTO0206 + ketamine.

BOLD signal was averaged within 3 ROIs (dACC, precuneus and thalamus). A mixed models ANCOVA examined the influence of Treatment (4 levels) and Time (2 levels: the average BOLD signal over the first and second 8 minutes of the active infusion). The baseline average was used as a covariate. The doses and ROIs were analysed separately. Within the model, pairwise contrasts of interest were AUTO0206 + ketamine versus placebo + ketamine.

**Results:** 23 subjects were randomised and 15 completed all 4 study scanning sessions, with dropouts mainly due to scanner technical issues, intolerance to ketamine, or excessive head movement. AUTO0206 was well tolerated with no serious or severe AEs attributed to study drug. Ketamine evoked rapid increases in BOLD signal in the 3 primary ROIs. In dACC, both doses of AUTO0206 attenuated the effect of ketamine compared to placebo, with pairwise effects of Treatment (β=−0.72; [95% CI -1.19 to -0.25] p=0.003) for the 800mg dose and (β= -0.49; [95% CI -0.97 to -0.02]) p=0.04) for the 2000mg dose. BOLD responses to ketamine in precuneus and thalamus were similar in magnitude, but shorter lasting than responses in dACC. AUTO0206 did not attenuate ketamine effects in precuneus. In thalamus AUTO0206 800mg lessened responses in the second 8 minutes at trend level significance (p=0.05) contributing to an overall Treatment by Time interaction (p=0.03). AUTO0206 800mg attenuated ketamine effects in all 12 secondary ROIs reaching significance in insula and right prefrontal cortex, again in the last 8 minutes.

**Discussion:** This study is the first evidence of a central effect of the novel Kv3 modulator, AUTO0206 in healthy humans. Based on evidence from rodent models, we suggest that the drug enhances the activity of GABA interneurons in cortical circuits, which opposes the effects of ketamine. The
induced by NMDA receptor antagonism. Further studies will investigate its mechanism, adult male Sprague Dawley rats were pre-treated with the drug (1, 3 or 10 mg/kg, PO) and sacrificed 1h later for the dissection of brain areas for molecular analysis. In order to test the ability of SEP-363856 to correct the alterations under a condition of reduced glutamate activity, adult female Lister Hooded rats were pre-treated with the drug (1, 3 or 10 mg/kg, PO) 60 minutes before an acute injection of PCP (2 mg/kg, i.p.). Locomotor activity was analysed during the following 90 minutes before sacrifice for the molecular analyses. Results: We found that the prefrontal cortex (PFC) showed the most significant changes in response to acute administration of SEP-363856. Indeed, the drug induced a significant up-regulation of a number of activity-dependent genes, such as Arc, Zif268, c-Fos and Npas4. We also found that the expression of the pool of BDNF transcripts with the long 3'UTR, characterized by a prominent dendritic localization, was significantly increased within the PFC of animals treated with SEP-363856. The prominent activation of PFC was associated with a significant increase of signalling pathways associated with glutamatergic and dopaminergic activity, including the phosphorylation levels of AMPA receptor subunit 1 (Glul), protein kinase B (Akt) and, to a lesser extent, the MAP kinases ERK1/2. When investigating the activity of the drug in the acute PCP model, we found that SEP-363856 at all doses attenuated PCP-induced hyperlocomotion. At the molecular level, we found that acute PCP injection up-regulated mRNA levels of activity-dependent genes (Arc, Zif268, c-Fos and Npas4) as well as of BDNF within PFC and these changes were also prevented by SEP-363856 at all doses.

Discussion: In summary, the results of our studies indicate that SEP-363856 has a rather selective activity on prefrontal cortex, by promoting rapid transcriptional mechanisms that may be related to its ability in modulating glutamatergic as well as dopaminergic pathways. Moreover, we found that SEP-363856 was able to counteract the behavioural and molecular effects induced by NMDA receptor antagonism. Further studies will investigate its ability to restore cognitive functions known to be impaired in schizophrenia.

T110. BIOEQUIVALENCE OF GENERIC AND BRAND NAME CLOZAPINE IN KOREAN SCHIZOPHRENIC PATIENTS: A RANDOMIZED, TWO-PERIOD, CROSSOVER STUDY

Abstract not included.

T111. TOBACCO CIGARETTE SMOKING IS ASSOCIATED WITH REDUCTIONS IN FUNCTIONAL CONNECTIVITY, ANATOMICAL CONNECTIVITY AND CORTICAL THICKNESS IN LARGE-SCALE NETWORKS

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Background: Abstinence from cigarette smoking is associated with disrupted interactions among the core cognitive resting state networks including the Salience (SN), Default mode (DMN) and Executive control (ECN). Unified multimodal methods [Resting state connectivity analysis, Diffusion Tensor Imaging (DTI) analysis, and cortical thickness analysis] were employed to test the hypothesis that the impact of cigarette smoking on the balance among these networks is due to alterations in white matter connectivity, functional connectivity and cortical thickness (CT) and that these metrics define fundamental differences between smokers and non-smokers.

Methods: Multimodal analyses of previously collected data via the Human Connectome Project were performed on 18 smokers and 18 age- and sex-matched nonsmoking controls. Resting state functional magnetic resonance imaging (fMRI) was used to compare SN-DMN and SN-ECN interactions between smokers and nonsmokers. The anatomy of these networks was then assessed using DTI and CT analyses. Finally, we computed a composite variable [resource allocation index (RAI)] that summed the combined strength of interactivity within these networks.

Results: Relative to control nonsmokers, resting state fMRI analysis revealed no difference in the coupling of networks. However, Resource Allocation Index computation of the inter-network coupling was significantly lower in the smokers. FA of right cingulum bundle was significantly lower in smokers as was thickness of left inferior parietal cortex, left and right precuneus, which are nodes of the ECN and DMN, respectively. Reduced RAI predicted lower cingulum bundle FA in smokers. Reduced thickness and FA were associated with degree of nicotine dependence as measured by the Fagerström score.

Discussion: Our results demonstrate that tobacco cigarette smoking is associated with alterations in all three independent metrics of brain function and anatomy. Whether these reductions are pre-existing, transient or permanent is not known. The observed disrupted salience in resting state networks, medial parietal thickness reductions and cingulum FA deficits may contribute to the cognitive and affective abnormalities that have been documented to occur in smokers.

T112. LEVEL OF COMPLIANCE WITH LONG ACTING INJECTIONS AND RISK OF HOSPITALIZATION

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Background: Previous studies showed a direct correlation between partial compliance with an oral antipsychotic medication and hospitalization risk among patients with schizophrenia across a continuum of compliance behavior. Long Acting Injections (LAIs) may enhance compliance and reduce