F231. GYM RATS: EXERCISE REVERSES COGNITIVE IMPAIRMENT IN THE PHENCYCLIDINE RAT MODEL OF SCHIZOPHRENIA
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Background: The cognitive deficits of schizophrenia have been identified as an unmet clinical need. They are predictive of functional outcome [Green et al., 2000] and quality of life [Fujii et al., 2004], yet there are no treatments able to normalise cognition in schizophrenia. There is increasing evidence that exercise is helpful for these symptoms [Geyer et al., 2012], but the systems involved remain enigmatic. Animal models can be used to scrutinise both the behavioural and biological effects of exercise. The sub-chronic phencyclidine (PCP) rat model for schizophrenia is a well-established and widely utilised model that is used to investigate schizophrenia-like cognitive deficits [Neill et al., 201]. This two-part study investigates whether voluntary wheel running is able to reverse cognitive impairment in the sub-chronic PCP rat model for schizophrenia, and how long the effect of exercise lasts.

Methods: Female Lister Hooded rats (n=80) were pseudo-randomised into four groups: vehicle-control; vehicle-exercise; PCP-control and PCP-exercise (n=20 per group). Rats were treated either with saline (vehicle) or PCP (2mg/kg, i.p. bi-daily, followed by a seven-day wash-out period). Vehicle and PCP exercise groups had access to a wheel for 1 hour a day, 5 days a week, for 6 weeks. The vehicle and PCP control groups were treated in the same way, but the wheels were locked. Rats were tested in the novel object recognition (NOR) memory paradigm pre-exercise (time point 1, T1) post-exercise (time point 2, T2), after two weeks rest (time point 3, T3) and four weeks rest (time point 4, T4). Half of the animals from each group (n=10 per group) were sacrificed post exercise (T2), and the remaining animals were sacrificed after 4 weeks rest. For each animal, 1 brain hemisphere was collected for protein analysis and 1 hemisphere was fixed for immunohistochemistry. Behavioural data were analysed using two-way ANOVA and post-hoc t-tests.

Results: Pre-exercise (T1), in the retention phase both vehicle groups were spent more time exploring the novel over the familiar object, an effect that was not seen in the PCP groups. Post-exercise (T2 & T3), in the retention phase both vehicle groups and the PCP exercise group spent more time exploring the novel over the familiar object, an effect that was not seen in the PCP-control group. Post-exercise (T4) in the retention phase both vehicle groups and the PCP-exercise group spent more time exploring the novel over the familiar object, an effect that was not seen in the PCP groups.

Discussion: Exercise is able to rescue the NOR cognitive deficit seen in the sub-chronic rat model for schizophrenia. This corresponds with human studies reporting positive effects of exercise in patients with schizophrenia and provides a potential tool to thoroughly investigate the pro-cognitive effects of exercise. The benefits of the exercise intervention were observed 2 weeks post-exercise and how long the effect of exercise lasts.

F232. A PHASE 3 STUDY TO DETERMINE THE ANTIPSYCHOTIC EFFICACY AND SAFETY OF ALKS 3831 IN ADULT PATIENTS WITH ACUTE EXACERBATION OF SCHIZOPHRENIA
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Background: ALKS 3831, currently under development for the treatment of schizophrenia, is composed of a flexible dose of olanzapine (OLZ) and a fixed dose of 10 mg of samidorphan. In a Phase 2 study, ALKS 3831 mitigated OLZ-associated weight gain and exhibited antipsychotic efficacy similar to OLZ alone. This Phase 3 study assessed antipsychotic efficacy and safety of ALKS 3831 in patients with acute exacerbation of schizophrenia.

Methods: This was an international (USA, Ukraine, Serbia, and Bulgaria), 4-week, randomised, double-blind, active and placebo (PBO)-controlled study of ALKS 3831 in patients with acute exacerbation of schizophrenia (ClinicalTrials.gov: NCT02634346). Eligible patients (N=403) were randomised 1:1:1 to receive either ALKS 3831, OLZ, or PBO. Patients were treated in an inpatient setting for the first 2 weeks of the study and could be treated as inpatients or outpatients for the remaining 2 weeks. Patients were excluded if they received OLZ within 6 months prior to screening. Antipsychotic efficacy was assessed using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), and CGI–Improvement (CGI-I) scales. Safety and tolerability were assessed as adverse events (AEs).

Results: Of 401 patients randomised and dosed to ALKS 3831, OLZ, and PBO, 91%, 89%, and 83% of patients, respectively, completed treatment. The most common reason for discontinuation was withdrawal by patient (6% in both the ALKS 3831 and PBO groups, and 7% in the OLZ group). Baseline characteristics were generally similar between groups; however, baseline mean body-mass index was higher in the OLZ group than in the ALKS 3831 group. Baseline mean ± standard deviation scores were 101.7 ± 11.9 for PANSS total score and 5.1 ± 0.7 for CGI-S score. The mean OLZ dose was 18.4 mg/day in both active treatment arms. Least squares (LS) mean difference ± standard error (SE) versus PBO from baseline to Week 4 in PANSS total score was −6.4 ± 1.8 (P<0.001) for the ALKS 3831 group and −5.3 ± 1.8 (P=0.004) for the OLZ group. LS mean difference ± SE vs PBO from baseline to Week 4 in CGI-S score was −0.38 ± 0.12 (P=0.002) for the ALKS 3831 group and −0.44 ± 0.12 (P<0.001) for the OLZ group. The percentage of patients with an improvement in PANSS response (≥30% improvement from baseline) at Week 4 was 60%, 54%, and 38% in the ALKS 3831, OLZ, and PBO groups, respectively. The percentage of patients with an improvement in CGI-I response (score of ≤2) at Week 4 was 58%, 51%, and 33% in the ALKS 3831, OLZ, and PBO groups, respectively. Discontinuation due to AEs was low in all groups. Common AEs (≥5%) included weight gain, somnolence, dry mouth, anxiety, headache, and schizophrenia.

Discussion: ALKS 3831 demonstrated greater antipsychotic efficacy than PBO, as measured by the PANSS and CGI-S scale, and was similar to the active control, OLZ. The safety profile of ALKS 3831 was similar to OLZ.

F233. NEGATIVE SYMPTOMS ARE INDEPENDENT MODERATOR FACTORS OF TREATMENT RESISTANT SCHIZOPHRENIA EFFECTS ON MULTIPLE CLINICAL, PSYCHOPATHOLOGICAL, COGNITIVE AND PSYCHOSOCIAL VARIABLES
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Background: Negative symptoms (NSs) are more severe in Treatment Resistant Schizophrenia (TRS) than Antipsychotic Responder Schizophrenia (ARS) patients. NSs are predictors of outcomes of neurological soft signs and functional capacity in TRS but not in ARS patients. The scope of this work is to clarify whether NSs effects are integral to or independent from the TRS diagnosis in our sample of patients.

Methods: 70 out of 206 eligible putative TRS and ARS patients were included (enrollment still ongoing). Patients were tested by the Neurological
Evaluation Scale (NES); the CGI-S; the PANSS; the Heinrichs’ Quality of Life Scale (QLS); the UCSD Performance-Based Skills Assessment (UPSA); the Personal and Social Performance (PSP) scale and Specific Level of Functioning (SLOF). Patients were subdivided in NSHigh (severe NSs) and NSLow (mild NSs) based on ROC curve-derived cut-off.

Results: At the Student’s t test, NSHigh had significantly lower scores than NSLow patients on: Verbal Fluency; QLS score; PSP score; UPSA Financial, Communication, and Family Skills; UPSA total score; all SLOF areas (except Area4). NSHigh patients had significantly higher scores than NSLow patients on CGI-S, PANSS Positive and General Psychopathology Subscale scores; and NES score.

Distribution of NS patients was significantly different between TRS/ARS diagnostic groups, as NSHigh patients were significantly more frequent in the TRS group (Pearson chi square: $\chi^2=5.51$, p=.001). Notably, mean PANSS Negative Subscale scores were significantly higher in TRS compared to ARS patients (Student’s t: $t_{1,58}=2.84$, p=.006).

Since multiple variables found to be significantly different in NSHigh vs. NSLow patients were also significantly different between TRS and ARS patients, the question arises whether the significant differences found between diagnostic groups may depend on the higher percentage of patients with more severe NSs in the TRS group. Therefore, a two-way ANOVA was carried out with dichotomous NS and Diagnosis variables as the independent variables. Outcomes on multiple clinical variables were significantly different among groups. A NS*Diagnosis interaction effect was found for NES score ($F_{1,58}=4.32$, p=.042, Visuospatial Memory, UPSA Transportation skills, and SLOF Area1). In all these cases, NSHigh/TRS patients performed significantly worse than the other patient groups; in the case of NES score, NSHigh/TRS patients score significantly higher than the other groups. Independent effect of either NSs or Diagnosis were also found for multiple variables, suggesting that NSs and Diagnosis may interact but their effects are not completely overlapping. To have a more deep comprehension of NS effects on diagnosis, we carried out a moderator regression analysis and an ANCOVA analysis that further confirmed the finding that NSs’ mediate Diagnosis effects on a number of clinical outcomes. Given that NSs largely affect clinical variables, we asked which distinct symptom may exert the greater impact on each of these variables. Therefore, we carried out a including the seven PANSS Negative Subscale items as the independent variables. The items that explained the highest variance in clinical variables were mostly Stereotyped Thinking (N7), Passive Social Withdrawal (N4), and Difficulty in Abstract Thinking (N5).

Discussion: These data suggest that NSs are both independent determinants and moderators of TRS/ARS diagnosis effect on multiple psychopathology, cognitive, and psychosocial factors. More impaired functions attributed to non-response to antipsychotics may depend on more severe NSs. However, only a subset of NSs appears to exert this action, possibly related to the multidimensional construct of these symptoms.

F235. DIFFERENTIAL EFFECTS OF ANTIPSYCHOTICS ON NEUROINFLAMMATION AND ENERGY SENSING IN A HYPOTHALAMIC CELL LINE

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Background: Antipsychotics (AP}s are the cornerstone of treatment for schizophrenia but cause serious metabolic side-effects. The hypothalamus is the primary brain region responsible for whole body energy regulation and disruptions in energy sensing (e.g. insulin signaling) and inflammation in this brain region have been implicated in the development of peripheral insulin resistance and obesity. Thus, it is possible that hypothalamic inflammation and disturbed energy sensing could be involved in AP-induced metabolic disturbances. Data in relation to AP-associated changes in inflammatory markers in schizophrenia has been inconsistent, owing in part to confounds of illness-related factors (e.g. diet, smoking) and secondary effects of weight gain. To our knowledge, direct effects of APs on hypothalamic cells in relation to insulin signaling and inflammation have not been examined.

Methods: To examine direct, molecular effects of APs in the hypothalamus, an immortalized rat hypothalamic cell line, rHypoE-19, was treated with olanzapine (dose range between 0.25–100 uM), clozapine (2.5–100 uM) or aripiprazole (5–20 uM). Western blotting was used to detect changes in the energy sensing protein AMPK, components of the insulin signaling pathway (AKT, GSK3B), and components of the mitogen activated-protein kinase (MAPK) pathway (ERK1/2, JNK, p38), the latter which are linked to inflammation. Quantitative real-time PCR was performed to determine changes in the mRNA expression of interleukin (IL)-6, IL-10 and brain derived neurotrophic factor (BDNF).

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