

trend in QIDS-J ($P=0.07$), an increasing trend in WHO-QOL ($P=0.07$) and a significant increase ($P=0.01$) in QPR-J before and after the intervention.

Discussion: These results suggest that exercise therapy may improve depressive symptoms, quality of life and recovery process in patients with bipolar depression without mediating weight changes.

Conclusion: Exercise may contribute to the functional recovery of patients with BD. We will further recruit the participants and conduct a more comprehensive analysis, including FAST, which was the primary outcome of this study.

References

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RELATIONSHIP BETWEEN CIRCADIAN AND SOCIAL RHYTHM REGULATION, CHRONOTYPE, COMT, CLOCK, GSK3- β GENE POLYMORPHISMS AND VALPROATE RESPONSE IN REMITTED BIPOLAR SUBJECTS

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Background: Bipolar disorder (BD) significantly disrupts biological rhythm [1, 2]. The first-line drugs used in the treatment are mood stabilizers, the most commonly used being lithium and valproic acid (VPA). Treatment response is variable and associated with many factors, including circadian rhythm and chronotype [4]. As shown in animal studies, VPA may interfere with circadian rhythm [3]. We therefore aimed to explore whether treatment response to VPA is related to (i) genetic variations [COMT Val158Met (rs4680), CLOCK 3111T/C (rs1801260), GSK3- β -50T/C (rs334558) polymorphisms], (ii) social and circadian rhythm and (iii) chronotype.

Methods: 94 patients aged between 18 and 65 with BD who had been using VPA for at least one month were included. Hamilton Depression Rating Scale (HAM-D), Young Mania Rating Scale, Biological Rhythm Interview for Assessment in Neuropsychiatry, Morningness Eveningness Questionnaire, Alda Scale, Social Rhythm Metric-5 (SRM-5) and Unified Parkinson's Disease Rating Scale-Motor Examination were employed. Kruskal-Wallis or One-Way ANOVA was used for comparisons among three polymorphism groups, Mann-Whitney U test or Independent Samples T-test for two groups, and Chi-Square Test or Fisher's Exact Test for dichotomous variables.

Results: Carriers of the C allele of the CLOCK 3111T/C polymorphism had later age of onset, lower number of previous mood episodes, more regular social and circadian rhythms and fewer daily mood swings. We also demonstrated that A/A genotype of COMT Val158Met polymorphism is advantageous, whereas C/T genotype of GSK3- β -50T/C polymorphism is disadvantageous in terms of response to VPA maintenance therapy. Moreover, regarding COMT Val158Met polymorphism, carriage of A allele has been associated with social rhythm irregularity and more frequent family history of a psychiatric disorder.

We found that the duration of the disease, the number of previous manic/hypomanic episodes, HAM-D total score, SRM-5 mood swing score, and duration of VPA exposure each have a negative correlation with the Alda Scale A score. Morningness chronotype was associated with more regular biological rhythm and better treatment response. Linear regression analyses showed that response to VPA treatment was predicted by a model consisting of the duration of disease, HAM-D total score, the number of previous manic/hypomanic episodes, SRM-5 mood swing score and duration of VPA exposure variables [$F(5)=9.34, R^2=0.32, p<0.001$].

Conclusions: These findings suggest that the C allele of the CLOCK 3111T/C polymorphism is protective in terms of the number of attacks, regularity of biological rhythm and mood swings. A/A genotype of COMT Val158Met

polymorphism and C/T genotype of GSK3- β -50T/C polymorphism are also associated with an improved response to VPA maintenance treatment. Treatment response is negatively correlated with the duration of disease, the number of previous manic/hypomanic episodes, HAM-D total score, SRM-5 mood swing score and duration of VPA exposure. Morningness is advantageous for regular biological rhythm and better response to VPA maintenance therapy. The total number of manic/hypomanic episodes, as well as total duration of VPA exposure, contributes to treatment response more predominantly than other independent variables included in the regression analyses.

References

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Conflict of interest

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TRKB MODULATOR OT-003 IMPROVES DEFICITS IN COGNITION AND NEGATIVE SYMPTOMS, AND ASSOCIATED BRAIN PATHOLOGY IN RAT SCHIZOPHRENIA MODELS

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Background: Pangea Bio is developing proprietary lead compound OT-003, an orally bioavailable small molecule Tropomyosin receptor kinase B (TrkB) modulator for neurological disorders including schizophrenia. The endogenous ligand of the TrkB receptor is brain-derived neurotrophic factor (BDNF). Physiological BDNF/TrkB signaling is crucial for neuronal development, survival, and plasticity. Aberrantly reduced BDNF/TrkB signaling is a hallmark of various neuropsychiatric diseases, including schizophrenia, where BDNF and TrkB levels are reduced. OT-003 binds and activates the TrkB receptor promoting neuronal survival, enhancing neuronal and synaptic plasticity, reducing neuro-inflammation, and normalising BDNF production.

Objectives: To assess efficacy and potency of OT-003 in modulating cognitive impairment and negative symptoms in preclinical schizophrenia models.

Methods: OT-003 was tested in the rat sub-chronic phencyclidine (scPCP) model which provides a translational model for schizophrenia through inducing cognitive deficits similar to those in patients as well as negative symptoms. Here, PCP, a NMDAR antagonist (2mg/kg, i.p.), or vehicle (0.9% saline) was administered bi-daily for 7 days to female Lister Hooded rats followed by a 7-day washout period. Subsequently OT-003 was administered orally once daily at 10 and 30mg/kg, and 3, 10 and 30mg/kg, for 3 weeks in two separate studies. In both studies, risperidone (0.1mg/kg, i.p.), administered acutely, served as a positive experimental control.

In the first study animals were tested in the novel object recognition (NOR) and social interaction (SI) tasks to assess cognitive and negative symptoms. To further test OT-003's ability to attenuate the scPCP-induced cognitive impairment with a more translational cognitive test, we conducted an attentional set shifting task (ASST) in study 2. ASST is the rodent analogue of Cambridge Neuropsychological Test Automated Battery Intra-/Extra-dimensional set shifting task (CANTAB ID/ED) and Wisconsin Card Sorting Test (WCST).

Post-mortem analysis was conducted with a focus on measuring number of parvalbumin-positive interneurons and protein levels of synaptic markers. All data are expressed as mean $\pm$ sem. Exploration time data from NOR were analysed via repeated measures general linear model (GLM). For the attentional set-shifting task, data for trials to criterion were analysed by repeated measures two-way ANOVA.

Results: OT-003 at 30mg/kg fully rescued scPCP-induced cognitive impairment