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Role of Orexin-A in the Treatment Response to Clozapine in Patients with Schizophrenia

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Background
Clozapine is the drug of choice for treatment-resistant schizophrenia(TRS). However, treatment resistance to clozapine has long remained a clinical dilemma. Although various combination and augmentation strategies, including antipsychotics, antidepressants, mood stabilizers, or electroconvulsive therapy (ECT), have been introduced as potential therapeutic approaches, none of them are consistently successful in treating clozapine-resistant individuals. This represents an unmet medical need for effectively treating patients with TRS. Despite the scarcity of research exploring the pathophysiology underlying clozapine resistance, emerging evidence has shown that TRS is associated with a multitude of neurobiological perturbations encompassing not only changes in dopaminergic (e.g. supersensitivity) and glutamate signaling but also changes in neuroinflammation and oxidative stress. Orexins (also known as hypocretins) sit at the nexus of neuropeptides that are implicated in the pathophysiology of schizophrenia. The elevation of orexin-A was less significant in patients taking clozapine relative to those taking other APDs, suggesting that clozapine treatment is associated with a distinct pattern of orexin-A regulation. However, whether orexin-A levels are related to the treatment response to clozapine is not yet known.

Aims & Objectives
This study aimed to examine the association of orexin-A levels with the treatment response in TRS patients taking clozapine more than 6 months. In the present study, we investigated the differences in orexin-A levels between clozapine-responsive and clozapine-resistant patients and examined the relationship between orexin-A levels and treatment response. We also examined the correlation of orexin-A levels with psychopathology and cognitive function.

Methods
We enrolled 100 clozapine-responsive and 62 clozapine-resistant patients with schizophrenia and compared the orexin-A levels between the two groups. Regression analysis was performed to determine the effect of orexin-A on psychotic remission. We also examined the correlations between orexin-A levels with psychopathology assessed by 18-item Brief Psychiatric Rating Scale (BPRS) and cognitive function assessed by Cogstate Battery.

Results
We found clozapine-responsive patients had higher plasma orexin-A levels than clozapine-resistant patients. Orexin-A level was the only factor significantly associated with psychotic remission after adjustment for potential confounders. Orexin-A levels were negatively correlated with the full BPRS-18 scale, and positive, negative, and general symptoms subscale scores. We also observed a positive correlation between orexin-A levels and verbal memory, visual learning and memory, and working memory function.

Discussion & Conclusion
Orexin-A levels differed between clozapine-responsive and clozapine-resistant patients with schizophrenia. Higher levels of orexin-A are associated with a more favorable clinical outcome in terms of psychopathology and cognitive function in patients treated by clozapine. Future prospective studies are warranted to understand the potential of orexin-A as a biomarker to predict clozapine response among patients with TRS.