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651. DISCOVERY OF OMICS-BIOMARKERS OF KETAMINE FOR TREATMENT RESPONSE IN DEPRESSION

*B. Baune, E. van Assche, KADS Study Group Australia
University of Münster, Department of Psychiatry, Münster, Germany

Background: DNA methylation is a biomarker suited to investigate dynamic processes, such as treatment response. For this analysis we focus on DNA methylation changes during a randomised controlled trial (RCT) in treatment resistant depressed patients comparing racemic ketamine (s.c.) versus midazolam (s.c.) (the Ketamine for Adult Depression Study - KADS). This clinical trial showed a stronger clinical response for patients in the response-guided dosing paradigm. We investigated epigenomic correlates of these dosing paradigms. We expected a correlation between dosing paradigm and DNA methylation changes with a stronger effect on DNA methylation changes for the response-guided paradigm.

Aims & Objectives: We performed a cross-sectional epigenome-wide association study (EWAS) at end of RCT treatment (after 4 weeks) comparing ketamine versus midazolam on the whole group and stratified by dosing paradigm. We also performed a paired longitudinal EWAS spanning from baseline to end of RCT treatment for the whole sample, then we repeated the analyses stratified by dosing paradigm (fixed and flexible dosing).

Method: DNA methylation data from 113 MDD patients in the KADS trial, treated with ketamine or midazolam for four weeks,

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were analyzed. A protocol amendment led to fixed 'lower' and flexible 'higher' dose cohorts. Cross-sectional EWAS compared ketamine and midazolam treatments across the whole sample, stratified by dosing paradigm. Longitudinal DNA methylation changes from baseline to week 4 were also examined, stratified by treatment and dosing group. Methylation data were collected using the Illumina Infinium MethylationEPIC 850k BeadChip. Differential methylation analysis was performed using limma and corrected for confounders. Significance was set at $p < 9.42 \times 10^{-8}$ or FDR-adjusted $p < 0.05$.

Results: While the overall analysis comparing DNA methylation for the ketamine vs. midazolam group in the entire cohort did not return any epigenome wide significant CpGs, the most significant CpG (cg11159519; $p = 2.38 \times 10^{-6}$) was in the KCNH1 gene, a potassium-channel gene.

The stratified analysis in the flexible dosing sub-cohort comparing ketamine vs. midazolam showed one epigenome-wide significant CpG, associated with the PDCD6-gene (cg15945600; $p = 7.28 \times 10^{-8}$; fdr p -val < 0.05). The analysis comparing both fixed-dosing conditions did not return any epigenome-wide significant CpGs. The analyses comparing flexible dosing (midazolam and ketamine) vs. fixed dosing (midazolam and ketamine) returned a suggestive hit, linked to the NEDD9 gene (cg20023762; $p = 1.11 \times 10^{-7}$; fdr p -val < 0.10). The longitudinal analyses stratified by dosing condition and therapy returned a statistically significant differentially methylated region (DMR) for the flexibly dosed ketamine condition only. This DMR is related to the CAPS2-gene (fdr p -val < 0.05).

Discussion & Conclusions: The results from these stratified analyses indicate that the clinically observed dose-response relationship for ketamine, with a higher anti-depressant effect for the flexible dosing paradigm, has a correlate at the DNA methylation level. DNA methylation changes were primarily observed in the higher-dose conditions, in particular for the patient group receiving high dose ketamine. Specifically, the genes PDCD6 and CAPS2 contribute to known biological pathways related to ketamine, e.g., the mTOR/VEGF/BDNF system. These results contribute to the growing field of pharmaco-epigenomics in Psychiatry and help to understand the dynamics of DNA-methylation changes in the background of ketamine-related treatment response.