Associations between antipsychotic induced weight gain and antipsychotic prescriptions: an observational retrospective cohort study [abstract]

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ASSOCIATIONS BETWEEN ANTIPSYCHOTIC INDUCED WEIGHT GAIN AND ANTIPSYCHOTIC PRESCRIPTIONS: AN OBSERVATIONAL RETROSPECTIVE COHORT STUDY

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Introduction: Antipsychotic agents are the first line treatment for various severe mental illnesses (SMI). Weight gain is a major side effect of antipsychotics [1,2], contributing to a higher risk of metabolic syndrome, reduced life expectancy and treatment non-adherence [3],[4]. In this study, we aimed to investigate and provide further evidence for factors associated with antipsychotic induced weight gain (AIWG).
Methods: We reviewed the health records of anyone who had been diagnosed for the first time with first episode psychosis, schizophrenia, schizoaffective disorder, and delusional disorder. We analysed body mass index (BMI) change in the 5-year period following the first prescription of antipsychotic medication. All individuals had taken an antipsychotic agent for at least 3 months. The 5-year follow-up point was anywhere between 2003 and 2023. We chose the pre-treatment weight value as the closest measure of weight before the initiation of an antipsychotic agent. It is to be noted that individuals may have multiple weight recordings in any given year.
Results: We identified 5618 people with the above diagnoses. There were 2,233 women (39.7%) and 3,385 men (60.3%). The mean age of the cohort at diagnosis was 16-75 years. The progression of BMI over time is displayed below, in Table One.

Time relative to initiation of antipsychotic agent	Mean BMI (kg / m2)	N (measures)
Pre-treatment	26.4	5,399
Up to 1 year post-treatment	29.3	4,049
1 - 3 years post-treatment	29.8	8,172
3 - 5 years post-treatment	30.3	7,713
Over 5 years post-treatment	30.4	32,330

At 5-year follow-up, 53.6% of individuals progressed from a normal BMI (18.5 - 24.9 kg/m2) to an overweight / obese BMI (25.0 or above) vs 43.7% who remained at a healthy BMI.83.1% of those with BMI ≥30kg/m2 stayed in this category. Individuals on second generation antipsychotics (SGA) were more likely to change from an normal BMI to an overweight / obese BMI, than those on first generation antipsychotics (FGA) (Hazard Ratio (HR) 2.0 vs 1.6). This was independent of age, duration of treatment (less than one year vs one year or more), sex and ethnicity. Individuals taking a greater number of antipsychotic agents were found to have an increased likelihood of changing from a normal to elevated BMI (1 agent: HR=1.4; 2 agents: HR =1.8: 3 agents: HR 2.2).
Conclusion: This study has identified an increased likelihood of weight gain with increasing antipsychotic polypharmacy, and with the prescription of a SGA vs FGA. This was found to be independent of other factors. We believe the next step is to build a combined 'polygenic / polyphenotypic risk score' , in order to identify patients possessing genetic risk factors for AIWG. Doing so would offer an increasingly personalised approach to antipsychotic prescribing, providing opportunities to minimise AIWG, by adapting and focusing interventions on higher risk individuals. This may improve treatment concordance and quality of engagement, while limiting the negative physical health outcomes associated with AIWG.
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TRANSCRIPTOMIC CHANGES ASSOCIATED WITH THE ANTIDEPRESSANT EFFECT OF CANNABIDIOL IN A GENETIC ANIMAL MODEL OF DEPRESSION

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Background: Major Depressive Disorder (MDD) is a major contributor to the global burden of disease, and results from the complex interplay of epigenetic, genetic and environmental factors. Although a wide variety of antidepressant drugs are available, they all present a delayed therapeutic effect, low remission ratio and lack of effect in one-third of patients.
Cannabidiol (CBD) is a non-psychostimulant compound derived from cannabis sativa, which has shown promising rapid-acting antidepressant profile in pre-clinical models, such as the established rat model of depression, Flinders Sensitive Line (FSL). Although CBD is known to target a range of receptors and enzymes, its precise mechanism of action remains unknown.
Objective: i) To reveal transcriptomic changes that may be linked to the antidepressant effect of CBD in the brain of FSL rats; ii) To evaluate to which extent these changes can substantiate the potential antidepressant effect of CBD.
Method: The Flinders Sensitive Line (FSL) and their controls, the Flinders Resistant Line (FRL), were used. FSL rats received one daily injection of 10mg/kg CBD or vehicle (i.p., 7 days). FRL rats were injected only with vehicle. One hour after the last injection, all animals were exposed to the open field-test (OFT, 10 min) and forced swim test (FST, 7 min). After this, rats were euthanized, and the prefrontal cortex was collected.
RNA was sequenced by Beijing Genomic Institute using DNA nanoball technology and the BGISEQ-500 system. Quality control, alignment, quantification and annotation of the reads was performed using the GenomeDK cluster. Reads were aligned to the NCBI RefSeq mRatBN7.2 genome assembly using Hisat2. Quantification and annotation were done using FeatureCounts. By principal component analysis, two possible outliers were identified. Count normalization by median of ratios method and differential gene expression analysis by Wald test was done using the R package "DESeq2". Following, gene set enrichment analysis (GSEA) was performed using the ClusterProfiler package in R. GSEA was performed using the KEGG, Reactome and GO databases. Gene set association analysis will soon be performed, integrating the gene expression results with previous GWASs of mental disease phenotypes, to uncover pathways that might be relevant to mental disease and the treatment of these. To further investigate the nature of the outliers, bulk deconvolution was performed using CibersortX, to reveal a potential error in the dissection of the animals and handling of samples, by estimating tissue or cell type abundance in each sample.
Results: CBD induced a significant antidepressant effect in the FST (decreased immobility time), without changing the locomotor activity in the OFT. 109 differentially expressed genes were found between the groups of primary interest (FSL-vehicle and FSL-CBD). GSEA showed enriched terms such as activation of "Activation of NMDA receptors and postsynaptic events", "Glutamatergic synapse", "positive regulation of dendrite morphogenesis", "Long term potentiation" and suppression of "axon ensheathment in central nervous system", "Parkinson disease", "ALS", "Alzheimer's disease".
Conclusions: Chronic CBD treatment significantly changed gene expression in rat prefrontal cortex, with enrichment of gene sets relevant to brain plasticity and neurodegenerative diseases.
No conflict of interest