

**Discussion:** Not only environment but also genotype should be considered in epigenetic studies. Furthermore, our results suggest that long-distance effects are present in GxE interactions. The epigenetic clock which mirrors prenatal environment is partially predictive for future development of the child. Lower epigenetic gestational age seems to be developmentally disadvantageous for boys, who in early childhood show greater psychiatric problems.

## 17. CANNABIDIOL AS A TREATMENT IN DIFFERENT STAGES OF PSYCHOSIS- EFFICACY AND MECHANISMS

Sagnik Bhattacharyya

*Institute of Psychiatry, King's College London*

**Overall Abstract:** While drugs that target the dopaminergic and glutamatergic neurotransmitter systems have been extensively investigated as treatments for psychosis, there has been increasing attention in recent years on the endocannabinoid system as a therapeutic target. The CB1 receptor, the main central cannabinoid receptor is ubiquitous and modulates the function of several neurotransmitters, including dopamine and glutamate. A growing body of evidence suggests that psychosis is associated with alterations in the endocannabinoid system, independent of exposure to cannabis.

The CB1 receptor is the main molecular target for delta-9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis. THC is responsible for the psychotogenic effects of cannabis, and is a partial agonist at the CB1 receptor. On the other hand, Cannabidiol (CBD), the second major constituent of cannabis is a non-psychoactive compound that may have an inverse agonist/antagonist effect at CB1 receptors, in addition to a range of other possible mechanisms of action. Interest in the therapeutic potential of CBD stemmed from evidence that it has broadly opposite effects to that of THC, at both the neural and the behavioural level in healthy individuals. Consistent with these results independent evidence that CBD has antipsychotic and anxiolytic properties in patients with mental health disorders has been accumulating. The absence of significant adverse effects associated with CBD, is a critical advantage in relation to the treatment of patients in the various stages of psychosis. Given its tolerability profile, CBD is a treatment of particular interest not just in those with chronic psychosis as in schizophrenia, but also in those in the earlier stages of psychosis. However, published evidence regarding the therapeutic efficacy of CBD as a treatment in psychosis has been limited except a small randomized clinical trial (RCT) some years ago (Leweke et al 2012). Furthermore, the mechanisms that may underlie the beneficial effects of CBD are unclear.

This symposium will bring together state of the art evidence regarding the efficacy of CBD in the different stages of psychosis – from those at clinical high-risk (CHR), through early psychosis to chronic schizophrenia. Furthermore, data from animal and human studies will be presented to give an understanding of the potential mechanisms that may underlie the therapeutic effects of CBD.

The first speaker (Prof Crippa) will set the scene by presenting evidence regarding the different potential mechanisms of action that may underlie the antipsychotic effect of CBD.

The second speaker (Prof McGuire) will present the results of a 6-week placebo-controlled RCT demonstrating the efficacy of CBD as an add-on to existing antipsychotic treatment in schizophrenia.

The third speaker (Dr. Ranganathan) will present the results from an ongoing, placebo-controlled RCT using an within-subject, crossover design to show the effects of 4-week CBD treatment on psychotic symptoms, cognition and electrophysiological markers in patients with established psychosis. Finally, the fourth speaker (Dr. Bhattacharyya) will present the results from a recently completed proof-of-concept study demonstrating the efficacy of short-term CBD treatment on symptoms and distress in CHR patients as well as on neurocognitive substrates implicated in the CHR state.

Evidence presented here will be discussed by Prof D'Souza, who is an internationally recognized expert in cannabinoid pharmacology and experimental therapeutics development.

## 17.1 A RANDOMIZED CONTROLLED TRIAL OF CANNABIDIOL IN SCHIZOPHRENIA

Philip McGuire<sup>\*.1</sup>, Philip Robson<sup>2</sup>, Wiesław Cubała<sup>3</sup>, Daniel Vasile<sup>4</sup>, Paul Morrison<sup>1</sup>, Rachel Barron<sup>2</sup>, Adam Taylor<sup>2</sup>, Stephen Wright<sup>2</sup>

<sup>1</sup>*Institute of Psychiatry, Psychology & Neuroscience, King's College London;* <sup>2</sup>*GW Pharmaceuticals;* <sup>3</sup>*Medical University of Gdańsk;*

<sup>4</sup>*Central Military Emergency University Hospital, Bucharest*

**Background:** Both preclinical and human research suggest that cannabidiol (CBD) has antipsychotic properties. This study assessed the safety and effectiveness of CBD in patients with schizophrenia.

**Methods:** Patients with schizophrenia (n=88) were randomized to receive CBD (1000 mg/day) or placebo alongside their existing antipsychotic medication for 6 weeks. Participants were assessed before and after treatment using the PANSS, BACS, GAF scales, and the CGI Improvement and Severity scales.

**Results:** Compared those given placebo, patients treated with CBD had lower levels of positive psychotic symptoms (PANSS; p=0.02), and were more likely to have been rated by clinicians as improved (CGI-I; p=0.02) and as not severely unwell (CGI-S; p=0.04). Patients who received CBD also showed trends for greater improvements in cognitive performance (BACS; p=0.07) and in overall functioning (GAF; p=0.08). There was no difference in the frequency of CBD of adverse events between CBD and placebo.

**Discussion:** These data suggest that CBD has beneficial effects in patients with schizophrenia and is not associated with significant adverse effects.

## 17.2 EFFICACY OF CANNABIDIOL IN THE TREATMENT OF EARLY PSYCHOSIS.

Mohini Ranganathan<sup>\*.1</sup>, Deepak D'Souza<sup>2</sup>, Jose Cortes-Briones<sup>1</sup>, Patrick Skosnik<sup>1</sup>

<sup>1</sup>*Yale University School of Medicine;* <sup>2</sup>*Yale University School of Medicine, VA Connecticut Healthcare System*

**Background:** Cannabidiol is a component of herbal cannabis, studied for a number of potential pharmaceutical indications, more recently, its potential anti-psychotic effects with an extremely favorable side effect profile. Cannabidiol content of cannabis may also attenuate the psychotic and cognitive effects associated with cannabis use. Early psychosis is associated with alterations in the endocannabinoid system and is marked by limited engagement in treatment, reluctance to use traditional antipsychotics, sensitivity to medication side effects and heavy cannabis use. Cannabidiol may thus represent a more acceptable and tolerable antipsychotic medication in this phase of illness with a novel mechanism of action.

**Methods:** Data will be presented from an ongoing double blind, placebo controlled, within subject, crossover study examining the effects of Cannabidiol (800mg/day) versus placebo in individuals within the first 7 years of their psychotic illness. Subjects participate in two treatment periods, each four weeks long separated by at least 2 weeks of washout.

**Results:** Data will be presented on the effects of Cannabidiol on psychotic symptoms (measured on the Positive and Negative Syndrome Scale), cognitive deficits (MATRICS battery), electrophysiological biomarkers of information processing (Resting EEG and ERPs relevant to psychosis and cannabinoids), metabolic parameters and general functioning.

**Discussion:** Cannabidiol is a novel drug that has shown potential efficacy in the treatment of psychotic symptoms. Early psychosis is a critical treatment period during which treatment engagement and adherence is critical and duration of untreated psychosis is associated with long term negative consequences. Cannabidiol may thus represent a more acceptable and tolerable medication to target this vulnerable population.