ABSTRACT: Cannabidiol (cbd) as an adjunctive therapy in schizophrenia: a multicenter, randomized controlled trial.

BACKGROUND

- Cannabidiol (CBD) has antipsychotic properties
- CBD attenuates both the experimental induction of psychotic symptoms by TCH and the adverse effects of THC on cognitive performance.

OBJECTIVE: *"…to explore the safety and effectiveness of CBD as adjunctive treatment in schizophrenia."*

METHODS

STUDY DESIGN

- Inclusion Criteria:
    - 18-65 years old
    - Diagnosis schizophrenia or a related psychotic disorder as defined by DMS-IV
    - Previously demonstrated at least a partial response to antipsychotic medication
    - Receiving stable dosage of antipsychotic medication for at least 4 weeks
- Exclusion Criteria:
    - PANSS score <60 at screening
    - Taking more than one antipsychotic medication
    - Presence of delirium, dementia, or any disorder or clinical finding that may have put the patient at risk, influenced the results, or have limited the patient's ability to participate
    - Pregnant, lactating, or planning pregnancy during or within 3 months of the completion of the trial
- Subjects from 15 hospital sites in UK (n=11), Romania (n=40), and Poland (n=37)
- After randomization, baseline assessments of symptoms, general functioning, cognitive performance, extrapyramidal signs were conducted and the patient's body weight, BMI, waist circumference, current substance use, HDL, liver enzymes, prolactin, inflammatory markers, CBD, and CBD metabolites were recorded.
- Reassessed using the same measures on day 8, 22, and 43 (+/- 3 days) and clinicians' impression of severity and improvement in the patient's condition and patient-reported or caregiver-reported impressions of general functioning and sleep were recorded
- Current substance use was reassessed at the end of treatment
- Patients assigned to receive 1000 mg/day of CBD (10 mL of a 100 mg/mL oral solution) or matching placebo administered in 2 divided doses (morning and evening)

OUTCOMES

- Key endpoints
    - PANSS Total, positive, negative, and general scores and responder analysis
    - Scale for Assessment of Negative Symptoms (SANS) score
    - Improvement score on the Clinical Global Impressions Scale (CGI-I)
    - Global Assessment of Functioning (GAF) scale score
    - Composite score on the Brief Assessment of Cognition in Schizophrenia (BACS)
- Endpoints of concern
    - Changes in severity scale of the CGI
    - Functioning and sleep scales of the participant and the Carer Global Impression of Change Scale
    - Simpson-Angus Scale
    - Body weight, waist measurement, BMI, HDL cholesterol

STATISTICS

- Intention to treat
- Change in PANSS total score from baseline to end point was analyzed using analysis of covariance, using age and baseline PANSS positive, negative, and general scores as covariates
- Number of responders per treatment group was analyzed using logistic regression, with age and baseline PANSS positive, negative, and general scores as covariates
- Post hoc analysis of the number of responders in each treatment group was conducted
- Other outcomes measures were quantified as change from baseline score and analyzed in a way similar to the PANSS total score

RESULTS

- 83 patients completed trial (Power of 85% reached at n=78 to detect a difference of 11 in PANSS total score between CBD and placebo on the change from baseline to end of treatment)
- Adverse events
    - All causes/GI: CBD 20.9%, Placebo 6.7%
    - Treatment related: CBD 18.6%, Placebo 6.7%
- Key Endpoint: *Symptom Severity Scale Scores:*
    - Positive psychotic symptoms were significantly reduced from baseline to end point in CBD group compared with placebo group (p=0.019; -1.4, 95% -2.5- -0.2)
    - Changes in levels of negative psychotic symptoms (SANS and negative PANSS subset, p= 0.117, p=0.965), overall psychopathology (PANSS total, p=0.133), and general psychopathology (PANSS general, p=0.196) over the treatment period were not significantly different between the CBD and placebo groups
    - Proportion of treatment responders (patients with an improvement ≥20% in PANSS total score) was higher in the CBD group than placebo but was not statistically significant (odds ratio= 2.62, 95% CI 0.86- 8.00 p=0.09)
    - Similar trend was evident when treatment response was defined as terms of improvement in the PANSS positive score (odds ratio=2.49, 95% CI 0.98-6.38, p=0.056)
- Key Endpoint: *CGI Improvement and Severity Ratings:*
    - A significantly higher proportion of patients in the CBD group were rated by their clinician as improved on the CGI-I scale compared with those in placebo (78.5% and 54.6%, treatment difference= -0.5, 95% CI -0.8- -0.1, p=0.018)
    - CBD group had higher proportions of patents in all three of the improvement sub-categories (very much improved, much improved, and minimally improved) compared with the placebo group
    - Group differences in longitudinal change in CGI-S scores were significant (treatment difference= -0.3, 95% CI -0.5-0.0, p=0.044)
- Level of Functioning: CBD group showed greater improvement in GAF scores but was non-significant (treatment difference= 3.0, 95% CI -0.4- 6.4, p-0.08)
- Cognitive Performance:
    - Greater improvement in the BACS composite score in the CBD group but was non-significant (treatment difference=1.31, 95% CI -0.10-2.72, p-0.068)
    - Individual ABCS domains showed significant improvement in motor speed in CBD group ($p<0.05$) and non-significant greater improvement in executive functions (p=0.068)
- No significant changes in prolactin levels, Simpson-Angus ratings, weight, waist circumference, liver function tests, inflammatory markers, HDL cholesterol, or quality or quantity of sleep

STRENGTHS

- Double-blind, control trial design
- Adherence was evaluated
- Unblinding was unlikely but their conclusions regarding this assumption are unclear
- Substance use was allowed similar to regular practice

LIMITATIONS

- Adherence was measured but not reported
- Relatively small sample size conducted overseas, standardization between sites not mentioned
- 8-weeks is likely long enough but not really well established for how long it would take to see effects
- Reporting mechanisms were very subjective, but difficult to avoid subjectivity
- A lot of manufacturer involvement in set up of trial
- Some comments and conclusions the author's came too were biased
- Emphasis on need for CBD in market seemed to shift from to treat negative symptoms (in the background) to treating positive symptoms (based on findings)
- Statistically significant findings did not seem to be clinically meaningful
- It was unclear as to what results were caregiver reported, patient reported, or clinician reported

CONCLUSION

CBD may be considered a somewhat safe adjunctive treatment for patients with schizophrenia who are at least partially controlled on an antipsychotic medication and have tried other traditional medication courses. This adjunctive therapy may be most beneficial in patients who need additional control with positive psychotic symptoms.

McGuire P, Robson P, Cubala WJ, Vasile D, Morrison PD, Barron R, et al. Cannabidiol (cbd) as an adjunctive therapy in schizophrenia: a multicenter, randomized controlled trial. Am J Psychiatry. 2018: 175(3); 225-231