Neuro-Oncology Practice

13(5), 1023–1024, 2026 | https://doi.org/10.1093/nop/npag025 | Advance Access publication March 22, 2026

Letter to the Editor

Cannabidiol for anxiety and depressive symptoms in primary brain tumors: Results from an early-terminated, placebo-controlled, crossover randomized clinical trial

Anxiety and depressive symptoms substantially affect quality of life in patients with a primary brain tumor.[1] Cannabis use is reported in 19% of these patients,[2] partly for symptom relief. Cannabidiol (CBD), a non-psychotropic cannabis component, has shown anxiolytic effects in animal models and small studies in healthy volunteers and patients with psychiatric disease.[3] No study has evaluated CBD in neuro-oncology patients.[4] We examined the effects of CBD on anxiety and depressive symptoms in patients with primary brain tumors and report adverse effects following early trial termination.

We initiated a double-blind, placebo-controlled crossover trial in adults with primary brain tumors with stable disease and clinically relevant anxiety at screening (State-Trait Anxiety Inventory—State Subscale (S-STAI) ≥44).

Patients were randomized to CBD 600 mg/day or a matched placebo for 3 weeks, followed by a >2-week washout before crossover. CBD tablets contained >99% CBD and <0.1% Δ-9-tetrahydrocannabinol (THC). Both CBD and the placebo were purchased from Echo Pharmaceuticals.

Outcomes were assessed at baseline and at completion of each treatment period: S-STAI (0-80) for anxiety (primary outcome), the Center for Epidemiologic Studies Depression scale (CES-D; 0-60) for depressive symptoms and the Common Terminology Criteria grading for adverse events. Success was claimed if the posterior probability of a non-zero treatment effect on anxiety symptoms was in favor of CBD at study completion and exceeded 97.5%, based on a Bayesian random effects model with weakly informative prior distributions. A sample size of 55 patients accrued in three years was prespecified to achieve 80% power assuming a Cohen's d of 0.5 and accounting for 10% loss to follow-up. For further details see the registered study protocol.[5]

Between March 2022 and May 2024, 20 patients with a mean age of 48 years (range 24-72) were randomized, 11 were female. Diagnoses included astrocytoma grade 2 (n=6) and grade 3 (n=2), oligodendroglioma grade 2 (n=5) and grade 3 (n=3), glioblastoma (n=3), ganglioglioma (n=1), and meningioma grade 2 (n=1, WHO 2021). Ten patients received CBD first. Fifteen patients completed both treatment periods. Discontinuation occurred in both arms and was due to excess anxiety, adverse events, study burden, or tumor progression. The trial was terminated early due to a low accrual rate.

Reductions in anxiety and depressive symptoms were generally larger under placebo than under CBD. The posterior probability that CBD improved symptoms was low (19% for anxiety and 11% for depressive symptoms). Posterior median treatment differences were +1.50 (95% credible interval for mean treatment effect: −1.85-4.92) for anxiety and +1.61 (−0.97-4.21) for depressive symptoms. Clinically significant anxiety was present in 50% after placebo and in 59% after CBD, see Figure 1. Adverse events were similar (CBD: one grade 1, one grade 2, and one grade 3; placebo: four grades 1, two grades 2). One patient developed a maculo-papular rash during CBD, possibly related to a carrier substance.

In conclusion, CBD 600 mg/day for three weeks, did not reduce anxiety or depressive symptoms compared with placebo, and more symptoms were observed during CBD compared to placebo. Low accrual likely reflected protocol burden, an overestimation of the number of patients willing and able to participate, and limited patient willingness to treat these symptoms with CBD in a research setting.

Based on our results and the low accrual rate, we discourage further investigation into CBD for anxiety and depressive symptoms in this population, as even high-dose CBD did not suggest symptom improvement.

Adverse events were mild and comparable across conditions, confirming previous findings.[6]

In this underpowered trial, oral CBD did not reduce anxiety or depressive symptoms in primary brain tumor patients compared with placebo.

Conflict of Interest Statement

The authors report no conflict of interest.

Funding

The Anita Veldman Foundation funded this investigator-initiated study, grant number CCA2018-2-17.

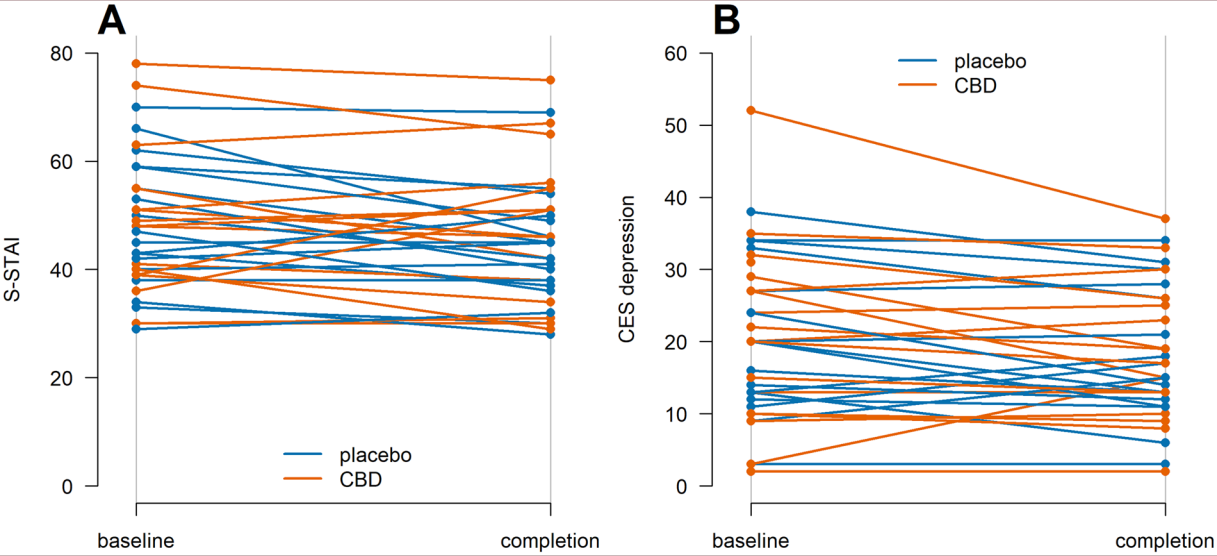

Figure 1. Measurements at completion and baseline for (A) anxiety (S-STAI) and (B) depressive symptoms (CES-D) during three weeks of oral cannabidiol (orange) and placebo (blue). Mean (SD) S-STAI decreased from 49.4 (12.5) at baseline to 43.4 (9.9) after three weeks during the placebo period, whereas scores remained stable during the CBD period (46.9 [13.5] at baseline to 47 [13.9] at three weeks). For CES-D, mean (SD) scores decreased from 20.7 (10.5) to 17.6 (8.9) during placebo and from 20.8 (12.3) to 18.5 (SD 9.5) during CBD.

Ethical Approval and Informed Consent

The study was approved by the Medical Ethics Review Committee (METC) of VUmc (approval number 2021.0056). Written informed consent was obtained from all participants prior to enrollment.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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