Research article

A randomized clinical trial of low-dose cannabis extract in Alzheimer's disease

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Abstract

Background: Preclinical and clinical evidence suggest that low-dose cannabinoids could ameliorate Alzheimer's disease (AD) signs and symptoms. We designed this trial to evaluate the safety and efficacy of low-dose THC-CBD balanced cannabinoid extract in the treatment of patients with AD-associated dementia.

Objective: The objective of this phase 2 trial was to evaluate the safety and efficacy of a balanced THC-CBD cannabinoid extract for symptomatic patients with AD.

Methods: A Phase 2, randomized, double-blind, placebo-controlled, clinical trial including patients between 60 and 80 years-old diagnosed with AD-associated dementia. For 26 weeks, participants orally received either placebo or THC-CBD extract (0.350 mg/THC and 0.245 mg/CBD), daily.

Results: At week 26, Mini-Mental State Exam total score was significantly higher in cannabis- when compared to placebo-treated patients, which was assessed using the mixed model analysis. No significant difference was detected between placebo and cannabis groups in terms of secondary outcomes and adverse events incidence.

Conclusions: To this date, this is the longest clinical trial evaluating cannabinoids effects on AD patients. We initially demonstrate that low-dose THC-CBD potentially can be an effective and safe therapeutic option for AD-related dementia. Nonetheless, larger and longer trials are necessary to confirm this finding and establish cannabinoid administration as therapy for AD dementia.

Trial Registration: The Brazilian Registry of Clinical Trials (ReBEC) registration #U1111-1258-2058 - REBEC (ensaiosclinicos.gov.br).

Keywords

Alzheimer's disease, cannabinoids, dementia, memory, Mini-Mental State Examination

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Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease worldwide, mainly affecting the elderly.[1] Pathological hallmarks of the disease are extensively known as the accumulation of amyloid-β (Aβ) oligomers and hyperphosphorylated tau protein. These two proteins are deleterious not only due to their presence in the brain, but mostly because they trigger a myriad of events that can exacerbate and contribute to further damage.[2] Neuroinflammation, gliosis, oxidative stress, insulin resistance, autophagy, and neurotransmitter dysfunction (e.g., cholinergic and glutamatergic) are some of the AD-associated features. All these detrimental alterations

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largely occur in brain regions that are related to cognitive function, which comprises memory, language, problem-solving, and other thinking abilities; consequently, the primary symptom of AD is cognitive decline, the foremost symptom of dementia.

Preclinical and clinical evidence suggest that there is an endocannabinoid system dysfunction associated with dementia[3–5] and, potentially, also in AD.[6,7] This concept is plausible because the cannabinoid receptors can be activated or inhibited thereby modulating synaptic plasticity and neurogenesis, among other molecular and cellular processes related to aging. A few examples of such processes include but are not limited to mitochondrial activity, glial activity, oxidative stress, and the clearance of damaged macromolecules.[8] The expression of cannabinoid receptors and endocannabinoid molecules can be decreased during aging.[9,10] Therefore, it can be hypothesized that treatment with exogenous cannabinoids could somehow compensate for the endocannabinoid decline observed in AD, with positive consequences for cognitive function. Indeed, this phenomenon has been observed in preclinical studies,[11] but it is yet to be proven in the clinical setting.

Recently, we reported a case study in which low-dose cannabinoid treatment was successfully applied to one patient with AD, in which beneficial effects were observed in mnemonic and non-mnemonic AD symptoms.[12] This single case, in which less than 1 mg of delta-9-tetrahydrocannabinol (THC) per day significantly sustained improved quality of life for over 2 years was the step stone for this clinical trial. The main assumption of this trial is that daily administration of low-dose phytocannabinoids—THC and cannabidiol (CBD)—may mitigate AD-associated cognitive impairment symptoms. Therefore, this phase 2 trial was designed to evaluate the safety and efficacy of a THC-CBD balanced cannabinoid extract for symptomatic AD patients.

Methods

Trial design and oversight

This is a 26-week, prospective, interventional, parallel, randomized, double-blind, placebo-controlled phase 2 trial that assessed the efficacy and safety of THC-CBD balanced cannabinoid extract in AD patients with dementia (Figure 1). This trial was not sponsored by any pharmaceutical company and was conducted in Foz do Iguaçu, PR, Brazil, being registered in May 2021 and ended in August 2022 (last patient completed last visit). The cannabis extract was produced and provided by the Brazilian patient's association "Cannabis Hope" (ABRACE; from Portuguese, *Associação Brasileira de Apoio Cannabis Esperança*), João Pessoa, PB, Brazil.

Standard Protocol Approvals, Registrations, and Patient Consents. This trial is in accordance with the previously approved ethical protocol (CAEE 098 13219.9.0000.0107) and followed international ethical guidelines, including but not limited to Declaration of Helsinki and International Conference on Harmonization E6 Good Clinical Practice Guidelines. This trial also followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines. All participants/caregivers provided written informed consent to publish their data. This trial was officially registered in the Brazilian platform ReBEC (Rede Brasileira de Ensaios Clínicos; # U1111-1258-2058). The Trial Protocol and Statistical Analysis Plan are available in Clinical Trial Material.

Eligibility criteria

Patients were recruited through social networks and media outlets, and their diagnosis was confirmed by the team neurologist. Our clinical team (physicians and pharmacists) was responsible for enrolling the patients. This trial included 29 male and female patients between 60 and 80 years old, 28 of whom received the treatment (see Figure 2; CONSORT diagram). Inclusions criteria were primarily age and AD-associated dementia diagnostic, according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[13] Additionally, the Clinical Dementia Rating (CDR) and the Functional Assessment Staging Test (FAST) were used to assess dementia progression. Furthermore, previous brain imaging tests, such as computed tomography or magnetic resonance imaging, that showed results compatible with AD, living in a community-based setting or care facility rather than living alone, and having a designated caregiver with enough interaction to be able to characterize a patient's symptoms and behavior were accounted for inclusion. Asymptomatic major depressive disorder, anxiety disorder, and stable diabetes were acceptable.

Exclusion criteria included other associated neurological conditions such as cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal pressure hydrocephalus, and brain tumor. Likewise, other peripheral and metabolic conditions that could cause dementia such as hypothyroidism, deficiency of vitamin B12, folic acid or niacin, hypercalcemia, neurosyphilis, and HIV infection. History of substance abuse and sequels due to substance abuse as well as psychosis, schizophrenia, epilepsy, or other psychiatric conditions were further exclusion factors.

Trial procedures

A third-party computer-generated table was used to carry out the block randomization (size 2; stratified by disease severity) for both treatment groups (www.sealedenvelope.com). Information about the allocated group (placebo or

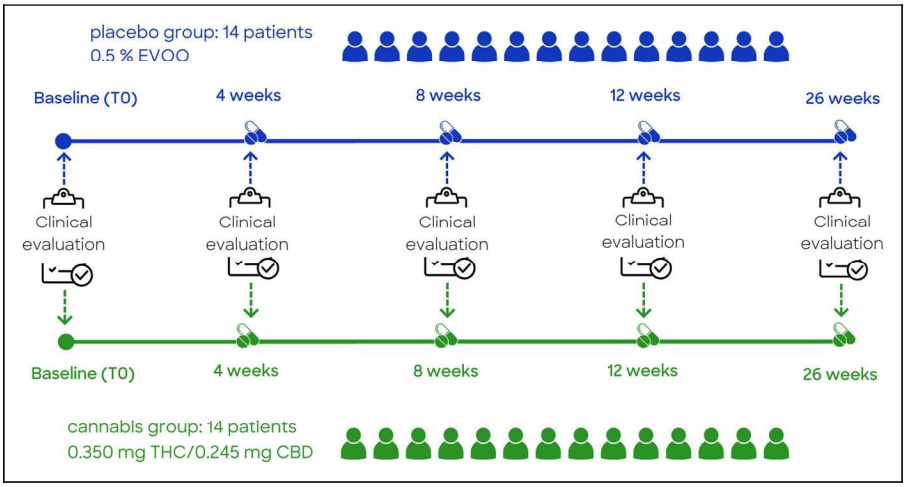

Figure 1. *Experimental design and timeline of the study.* The treatment timeline and clinical evaluations for two groups: the placebo group (14 patients receiving 0.5% Extra Virgin Olive Oil; EVOO) and the cannabis group (14 patients receiving 0.350 mg THC/0.245 mg CBD in 0.5% EVOO). Both groups underwent clinical evaluations at baseline (T0), 4 weeks, 8 weeks, 12 weeks, and 26 weeks (trial endpoint).

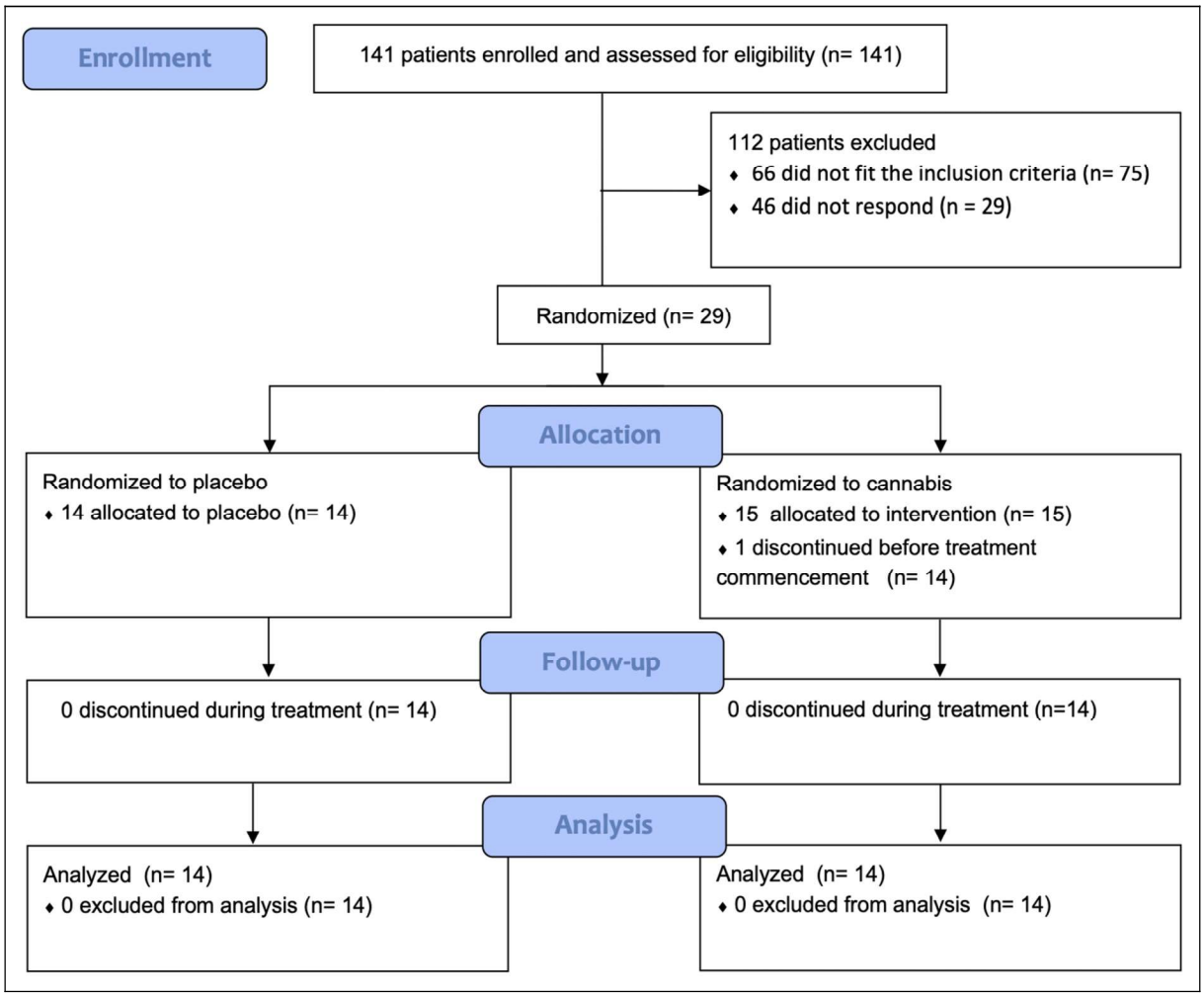

Figure 2. *Patient enrollment and randomization diagram.* Out of 141 assessed patients, 112 were excluded due to non-eligibility or non-response. The remaining 29 patients were randomized into placebo (14) and cannabis (15) groups, with 1 patient discontinuing from the cannabis group before treatment. All remaining patients completed the study and data was analyzed.

cannabis) was written on cards and placed into sequentially numbered opaque sealed envelopes. Researchers unaware of the individual eligibility assessment conducted patients' randomization, code assignment, and treatment distribution. Envelopes were unsealed on data analysis day.

Operators, subjects, and caregivers were all blinded to the protocol, having access only to the patient's identification code; thus, none of them were aware of the treatment allocation. Patients who met the eligibility criteria were randomly assigned in a 1:1 ratio to receive 0.35 ml of a THC-CBD balanced cannabinoid extract (0.350 mg of THC and 0.245 mg of CBD) or placebo, administered orally, once per day, for 26 weeks (i.e., 6 months or trial endpoint). The vehicle for both solutions was 0.5% acidity extra virgin olive oil (EVOO). Sensorial tests were performed among a different group of volunteers, before the trial, to guarantee that no odor and/or taste differences existed between solutions. Clinical evaluations were performed at baseline (T0), 4 weeks, 8 weeks, 12 weeks, and 26 weeks after treatment (Figure 1).

In this trial, patients received the maximum daily volume of 0.35 ml (placebo or cannabis extract). Patients who completed the double-blind period were given the option to participate in a 6-month open-label period. This report only includes results from the double-blind, placebo-controlled period of the trial, which was uniform for all completing participants. The main objective of this trial was to test the hypothesis that the low-dose cannabis extract would ameliorate AD-associated cognitive impairment in patients, when compared to placebo.

Outcome measure

The primary efficacy outcome measure considered the change from baseline over time through week 26 and was determined by the difference in score at the trial endpoint between placebo- and cannabis-treated groups on the 14-itemized cognitive scale of the Mini-Mental State Exam (MMSE; scores range from 0 to 30, with lower scores indicating cognitive decline). Secondary cognitive efficacy outcome measures included scores on the 14-itemized Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog; scores range from 0 to 90, with higher scores indicating cognitive impairment) and the Dementia Severity Rating Scale (DSRS; scores range from 0 to 54, with higher scores indicating cognitive impairment). Secondary non-cognitive measures included: the Cornell Scale for Depression in Dementia (CSDD; 19 questions applied to caregiver and patient, with scores higher than 10 indicating probable major depression and greater than 18 as major depression), the Geriatric Depression Scale (GDS; evaluates 15 symptoms that strongly correlate to depression), the Quality of Life in Alzheimer's Disease scale (QoL-AD; evaluates 13 items ranging from a 13 to 52 score, with higher scores indicating better quality of life), the Pittsburgh Sleep Quality Index (PSQI; a 19 question self-questionnaire and 5 questions applied to caregiver evaluating sleep: quality, latency, duration, efficiency, disturbances, daytime dysfunction, as well as use of sleep medications), the Epworth Sleepiness Scale (ESS; evaluates 8 items with scores ranging from 0 to 24, in which scores higher than 10 indicate sleep disturbances), and the Neuropsychiatric Inventory-Questionnaire (NPI-Q; evaluates 12 symptoms in the following domains: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviors, nocturnal behavioral disorders, and appetite disorders).

Safety assessments

Primarily, adverse event questionnaires were applied to patients and caregivers in order to determine occurrence and incidence of adverse events. Secondary safety assessments consisted of routine physical and neurological examinations and clinical laboratory tests. Safety assessments were performed by site investigators who were not conducting the efficacy assessments, and therefore were also blind to the group assignments. Adverse events severity was classified using the 5.0 version of the Common Terminology Criteria for Adverse Events (CTCAE).[14]

Statistical analysis

We calculated that enrolling 35 patients would provide 80% power (two-sided α=0.05; considering as well the Cohen's D effect size of 0.50) to detect a specified difference in the primary outcome. The calculated ideal target enrollment was 37 patients, allowing for up to 5% dropout. 1) Efficacy analyses were conducted using data from subjects who had a baseline and at least one post-baseline score, following the modified Intention-To-Treat (ITT) principle. An interim analysis was not performed because the a priori established allocated time for patient recruitment and clinical evaluation was not considered long-term. Additionally, there was no reason for interrupting the trial before the proposed endpoint. To assess significant differences between treatment outcomes over time, we constructed nine Mixed-effects Models for Repeated Measures (MMRM). Each model included the term "group" (placebo and cannabis) as a fixed effect, while the response variables were the scores of each addressed index (MMSE, ADAS-Cog, DSRS, CSDD, GDS, QoL-AD, PSQI, ESS, and NPI-Q), individually delineated in each model. Repeated measures over time were modeled categorically, accounting for within-subject correlation from repeated assessments and using an unstructured covariance matrix. Baseline scores for each outcome were structured using the T0 interval of each index and included as covariates to adjust for initial differences between participants (e.g., when T0 exceeded the median, the volunteer baseline was categorized as "high", while values below

Table 1. *Demographic and clinical baseline characteristics of patients in the trial.*

Study Variables	placebo (n = 14)	cannabis (n = 14)	p
Age (y)	73.6 ± 5.5	73.1 ± 5.7	0.664
Sex			1.000
Male	6 (43.0)	6 (43.0)	
Female	8 (57.0)	8 (57.0)	
Race[a]			0.595
White	12 (86)	13 (93)	
Black	1 (7.0)	1 (7.0)	
Asian	0 (0.0)	0 (0.0)	
Indigenous	1 (7.0)	0 (0.0)	
Educational level[b]			0.712
Elementary uncompleted	5 (36.0)	6 (43.0)	
Elementary completed	5 (36.0)	3 (21.0)	
Secondary uncompleted	0 (0.0)	0 (0.0)	
Secondary completed	2 (14.0)	2 (14.0)	
College completed	0 (0.0)	1 (7.0)	
Graduate uncompleted	1 (7.0)	2 (14.0)	
Graduate completed	1 (7.0)	0 (0.0)	
Monthly income[c]			0.296
up to 1 minimum wage	0 (0.0)	1 (7.0)	
1–2 minimum wages	4 (29.0)	2 (14.0)	
2–7 minimum wages	8 (57.0)	10 (71.4)	
>7 minimum wages	2 (14.0)	1 (7.0)	
MMSE classification			1.000
Mild	3 (21.0)	3 (21.0)	
Moderate	10 (71.0)	10 (71.0)	
Severe	1 (7.0)	1 (7.0)	
Time of diagnosis (years)	3.0 ± 1.0	4.0 ± 1.0	0.425
CDR stage			0.787
None (0)	0 (0.0)	0 (0.0)	
Very Mild (0.5)	1 (7.0)	1 (7.0)	
Mild (1)	4 (28.5)	4 (28.5)	
Moderate (2)	9 (64.5)	8 (57)	
Severe (3)	0 (0.0)	1 (7.0)	
Smoking status			0.456
Yes	4 (29.0)	5 (36.0	
No	9 (64.0)	8(57.0)	
Former smoker	1 (7.0)	1 (7.0)	
Alcohol consumption			0.315
Yes	11 (78.0)	11(78.0)	
No	3 (22.0)	3 (22.0)	
Antidementia therapy at baseline			
Acetylcholinesterase inhibitor alone	1 (7.1)	4 (28.6)	0.180
Memantine alone	3 (21.4)	1 (7.1)	0.276
Acetylcholinesterase inhibitor and Memantine	6 (42.6)	4 (28.6)	0.682
None	4 (28.6)	5 (35.7)	
MMSE score	13.1 (6.2)	16.0 (3.6)	0.181
ADAS-Cog score	34.1 (17.7)	29.2 (10.4)	0.096
DSRS score	27.3 (5.7)	23.4 (4.6)	0.815
CSDD score	14.5 (5.3)	11.7 (4.4)	0.203
GDS score	4.0 (2.4)	4.5 (2.9)	0.886
QoL-AD score	34.3 (7.1)	33.4 (3.9)	0.008
PSQI score	5.6 (2.5)	4.7 (2.5)	0.874
ESS score	11.5 (4.6)	8.5 (5.6)	0.345
NPI-Q score	36.2 (21.3)	25.2 (13.8)	0.209

Two-sided Chi-square (χ^2) test was performed for proportion comparisons; Independent samples t test was performed for mean comparisons; $p < 0.05$ set as significant;
[a]self-reported.
[b]Based on the Brazilian educational system.
[c]Based on the Brazilian minimum wage (approximately U$ 230).

the median were categorized as "low"). If under unstructured covariance matrix convergence failed, the following tests were sequentially applied: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure.[15] The models were implemented in the statistical software R using the MMRM package.[16] 2) Adverse events analysis were conducted applying two-tailed Fisher's exact test to compare the frequency between the cannabis and placebo groups, given the occurrence of low or even zero counts in several categories. Furthermore, 95% confidence intervals for the differences in proportions were calculated using the Wald approach for independent samples and exact p-values reported alongside these intervals.[17] Confidence intervals including zero were interpreted as indication of no meaningful difference between groups. In all statistical analysis alpha levels were set at 0.05 and the full statistical plan for this trial can be assessed on Supplemental Material eSAP1.

Results

Trial population

Of 141 patients who completed screening, 29 met the inclusion criteria. Of these 29 patients, 14 were randomly assigned to receive placebo and 15 to receive the cannabis extract. One patient of the cannabis group abandoned the study before receiving any treatment (Figure 2). Trial screening started before COVID-19 pandemic and was initiated while we were facing it, representing a challenge for elderly people (high-risk group) to travel for measurements, posing limitations for trial adherence. There were no significant differences between groups regarding the patient's baseline characteristics (e.g., age, sex, race, educational level, or monthly income). In the placebo and cannabis groups, 73.6 ± 5.5 and 73.1 ± 5.7 years-old was the mean age, 57.0% and 57.0% were women, 86.0% and 93.0% were white, respectively (Table 1). The MMSE gross value score baseline was 16.0 ± 3.6 for the placebo group and 13.1 ± 6.2 for the cannabis group, while the ADAS-Cog score baseline was 29.2 ± 10.4 and 34.1 ±

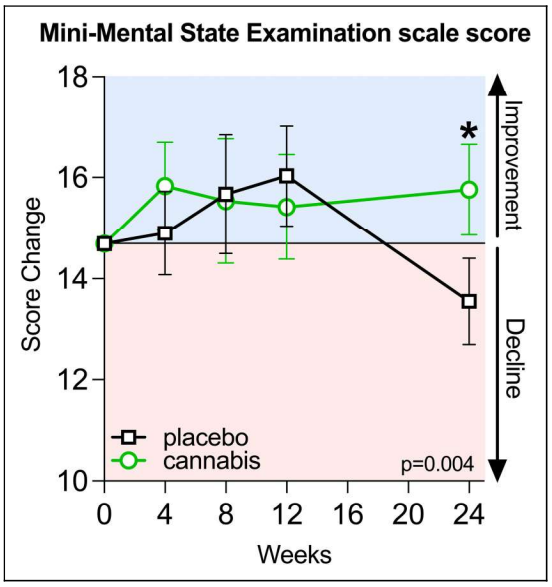

Figure 3. *Change in Mini-Mental State Examination (MMSE) scores over 26 weeks in cannabis versus placebo groups.* Figure shows the change in MMSE adjusted scores over 26 weeks for patients treated with cannabis (green line) and placebo (black line). The cannabis group exhibited a significant improvement in cognitive function, with scores increasing over time (*p = 0.004). In contrast, the placebo group showed a decline in MMSE scores over the same period, indicating worsening cognitive function. Error bars represent standard error of the mean (SEM).

17.7, for each group respectively (Table 1). Noteworthy, all patients in this trial had symptoms sufficiently severe to meet diagnostic criteria for AD-associated dementia. Among all patients that concluded the trial, 2 were staged very mild, 8 mild, 17 moderate, and 1 as severe, according to CDR. Also, 5 patients were taking acetylcholinesterase inhibitors, 4 memantine, 10 the combination of both drugs, and 9 were not medicated at all when the trial started. All medicated patients kept their medicine intake throughout the trial. We have not observed any proven synergisms or particular side effects on people taking medication versus the ones receiving the cannabis extract or placebo only. Additional clinical baseline and demographic characteristics of the patients are presented in Table 1.

Primary outcome

Results of the MMSE, primary outcome, considered change in score from baseline to week 26. At the trial endpoint, there was a significant difference in score between placebo- and cannabis-treated groups (Figure 3). The placebo group MMSE score was reduced to −1.08 (−2.12 to −0.05) and cannabis group MMSE score was increased to 0.67 (−1.76 to 3.10), a difference of about 1.7 points higher for the cannabis group on the 30 points scale over 6 months, when compared to placebo. The between-group difference was statistically significant (p = 0.0046), with an estimated effect size of Cohen's D = 0.63 (95% CI: −0.13 to +1.39), indicating a moderate effect favoring the cannabis group, although the confidence interval encompassed zero. The calculated Number Needed to Treat (NNT) to achieve one additional responder was 3.2 (95% CI: −1.4 to 17.6) and the Absolute Risk Reduction (ARR) for this outcome was −0.31. Using responder analysis, in which a clinically meaningful improvement was defined as a score at week 26 equal to or greater than the baseline MMSE score, 64.2% of patients in the cannabis group met the criterion, compared to 33.3% in the placebo group, that means patients on cannabis were twice as likely to maintain or improve their scores as those on placebo, indicating the low-dose cannabinoid extract treatment was effective in mitigating AD-associated cognitive decline.

Secondary outcome

No statistical differences were observed between the placebo and cannabis groups in any of the secondary outcomes analyzed. All the scores, mean differences, 95% confidence intervals, and p values for the ADAS-Cog, DSRS, CSDD, GDS, QoL-AD, PSQI, ESS, and NPI-Q scales are shown in Table 2.

Adverse events

Every patient experienced at least one adverse event during the trial course while no significant difference was detected between placebo and cannabis groups in terms of adverse events incidence, as shown in Table 3. Though, the most frequently observed adverse events, as well as the most variable in between placebo and cannabis groups were respectively as follows: anxiety (50.0% and 50.0%), increased appetite (64.0% and 57.0%), weight gain (24.0% and 50.0%), diarrhea (29.0% and 29.0%), loss of balance (43.0% and 36.0%), mental confusion (43.0% and 50.0%), disorientation (36.0% and 50.0%), depression (43.0% and 22.0%), headache (7.0% and 29.0%), somnolence (29.0% and 57.0%), and paranoia (7.0% and 36.0%). Caregivers reported episodes where patients described unreal visions or perceptions, subjectively classified as non-psychotic hallucinations. It is of our belief those were disease-related manifestations, as such symptoms are common for this population and even though frequency appears to be higher in cannabis group, no significant intergroup difference was found. All adverse events experienced by patients, mean differences, 95% confidence intervals, and p values are summarized in Table 3.

Discussion

In this Phase 2 randomized clinical trial, AD patients who received low doses of a balanced cannabis extract

Table 2. *Primary and secondary outcomes based on intention-to-treat analysis for patients with data outcome available at week 26.*

	placebo (n = 14)		cannabis (n = 14)			
	26 weeks		26 weeks			
	Baseline (SD)	Adjusted mean difference (95% CI)	Baseline (SD)	Adjusted mean (95% CI)	Adjusted mean difference (95% CI)	p
MMSE score[a]	16.0 (3.6)	13.5 (11.7–15.3)	13.1 (6.2)	15.7 (13.8–17.6)	−2.2 (−0.4–4.8)	0.004
ADAS-Cog score[b]	29.2 (10.4)	34.6 (28.4–40.8)	34.1 (17.7)	35.5 (29.0–41.9)	−0.8 (−9.9–8.1)	0.435
DSRS score[c]	23.4 (4.6)	26.6 (22.8–30.3)	27.3 (5.7)	25.4 (21.5–29.3)	1.2 (−4.3–6.7)	0.104
CSDD score[d]	11.7 (4.4)	6.7 (3.1–10.3)	14.5 (5.3)	7.1 (3.5–10.7)	−0.4 (−5.9–5.0)	0.214
GDS score[e]	4.5 (2.9)	4.2 (2.9–5.5)	4.0 (2.4)	4.3 (2.9–5.7)	−0.05 (−1.9–1.5)	0.715
QoL-AD score[f]	33.4 (3.9)	34.9 (33.8–36.0)	34.3 (7.1)	34.2 (33.1–35.4)	0.6 (−0.9–2.2)	0.252
PSQI score[g]	4.7 (2.5)	5.5 (4.4–6.7)	5.6 (2.5)	4.3 (3.1–5.1)	1.2 (−0.4–2.9)	0.743
ESS score[h]	8.5 (5.6)	7.7 (5.5–9.9)	11.5 (4.6)	7.8 (5.5–10.1)	−0.07 (−3.3–3.1)	0.164
NPI-Q score[i]	25.2 (13.8)	21.9 (13.3–30.5)	36.2 (21.3)	21.1 (11.7–30.6)	0.7 (−12.3–13.8)	0.813

Mixed-effects Models for Repeated Measures (MMRM) were used to assess between-group differences (cannabis group minus placebo group) in the adjusted changes from baseline to week 26. The dependent variable was the change from the baseline score at each post-baseline visit during the treatment period. Baseline scores of each assessment tool are presented in this table as gross values and were employed as covariates in this model. < 0.05 set as significant.

[a]The primary outcome was the change from baseline to week 26 in the Mini-Mental State Examination (MMSE) score, ranging from 0 to 30, with lower scores indicating worse functioning.

[b]Scores on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) range from 0 to 90, with higher scores indicating greater cognitive impairment.

[c]Scores on the Dementia Severity Rating Scale (DSRS) range from 0 to 54, with higher scores indicating worse functioning.

[d]Scores on the Cornell Scale for Depression in Dementia (CSDD) range from 0 to 38, with higher scores indicating worse depressive symptoms.

[e]Scores on the Geriatric Depression Scale (GDS) range from 0 to 15, with higher scores indicating more severe depression.

[f]Scores on the Quality of Life in Alzheimer's Disease (QoL-AD) range from 13 to 52, with higher scores indicating better quality of life.

[g]Scores on the Pittsburgh Sleep Quality Index (PSQI) range from 0 to 21, with higher scores indicating worse quality of sleep.

[h]Scores on the Epworth Sleepiness Scale (ESS) range from 0 to 24, with higher scores indicating more severe sleepiness.

[i]Scores on the Neuropsychiatric Inventory (NPI-Q) range from 0 to 144, with higher scores indicating worse functioning.

(0.350 mg/THC; 0.245 mg/CBD) exhibited a significant relief of cognitive impairment demonstrated by the primary outcome (MMSE), when compared with the placebo group at the trial endpoint. We report a 1.7-point positive difference at the MMSE score favoring the cannabis group over the placebo group at week 26, which might seem a modest effect, yet must be compared to disease natural course and/or existing non-modifying AD-therapy. AD patients on average decline about 3 to 4 MMSE points per year, which corresponds to approximately 1.5 to 2 points over 6 months.[18] Considering AD progression accentuated cognitive decline, we achieved with cannabis treatment remarkable disease stabilization in a half-year period, superior effect compared to cholinergic drugs, for instance, recognized to slow decline in 1 to 2 MMSE points per year,[19] with virtually no severe adverse events.

All patients experienced at least one adverse event throughout the trial period among all the mild to moderate adverse events reported, though no patients withdrew from this trial due to adverse events. We report that anxiety, appetite increase, loss of balance, and mental confusion, were the most frequently adverse events cited for both groups. While the placebo group seemed to exhibit higher incidence of depression, more patients at the cannabis group reported disorientation, headache, paranoia, somnolence, dry mouth and weight gain, yet none of these differences were statistically significant. Indeed, a number of these adverse events could have been considered expected since they are well-known cannabinoid effects, notwithstanding patients described milder cannabinoid-related adverse events in comparison to those previously reported,[20] or associated with other AD medications. Since nearly all adverse events occurred during the first week of treatment, the regimen appears to be well-tolerated with minimal discomfort, following a short adaptation period. It is also necessary to acknowledge, given the uncertain ambiance for these unvaccinated senior patients during the COVID-19 pandemic, at least in part these symptoms might not have been caused by the treatment. Cannabis has in general a very safe profile, especially at the very low doses we administered, no major or unknown safety issue was encountered. As it would be also expected for other newly-introduced treatments, we cannot completely rule out the possibility of adverse events occurring with this type of treatment, posing a modest limitation of this trial.

Another limitation that should be considered is the possible learning bias of repeated MMSE testing. Even though it could lead to gradual score improvements due to familiarity (especially accounting for possible treatment effectiveness over trial period), the mixed model inherently accounts for within-patient repeated measurements and the placebo group significant MMSE scores decline at week 26 was not prevented, as previously shown,[21,22]

Table 3. *Summary of adverse events occurring in either trial group.*

Event	placebo (n = 14) no. (%)	cannabis (n = 14) no. (%)	Adjusted mean difference (95% CI)	p
Hallucinations	2 (14.0)	4 (29.0)	−15.6–44.2	0.648
Anxiety	7 (50.0)	7 (50.0)	−37.0–37.0	1.000
Asthenia	4 (29.0)	4 (29.0)	−33.5–33.5	1.000
Appetite increase	9 (64.0)	8 (57.0)	−43.2–28.9	1.000
Weight gain	3 (24.0)	7 (50.0)	−5.3–62.5	0.236
Dry mouth	5 (36.0)	6 (43.0)	−28.9–43.2	1.000
Headache	1 (7.0)	4 (29.0)	−5.8–48.7	0.325
Mental confusion	6 (43.0)	7 (50.0)	−29.7–44.0	1.000
Depression	6 (43.0)	3 (22.0)	−55.1–12.2	0.419
Disorientation	5 (36.0)	7 (50.0)	−22.0–50.6	0.703
Diarrhea	4 (29.0)	4 (29.0)	−33.5–33.5	1.000
Dyspnea	0 (0.0)	2 (15.0)	−4.0–32.6	0.481
Euphoria	2 (15.0)	4 (29.0)	−15.6–44.2	0.648
Fatigue	2 (15.0)	4 (29.0)	−15.6–44.2	0.648
Nausea	3 (24.0)	4 (29.0)	−24.8–39.1	1.000
Paranoia or psychosis	1 (7.0)	5 (36.0)	0.1–57.1	0.164
Loss of balance	6 (43.0)	5 (36.0)	−43.2–28.9	1.000
Somnolence	4 (29.0)	8 (57.0)	−6.5–63.7	0.251
Dizziness	3 (24.0)	4 (29.0)	−24.8–39.1	1.000
Vomiting	2 (15.0)	0 (0.0)	−32.6–4.0	0.481
Endocrine and metabolic effects	1 (7.0)	1 (7.0)	−19.1–19.1	1.000
Cardiocirculatory effects	2 (15.0)	2 (15.0)	−25.9–25.9	1.000
Kidney effects	0 (0.0)	1 (7.0)	−6.3–20.6	1.000
Dermatological effects	1 (7.0)	2 (15.0)	−15.6–29.9	1.000
Infections	1 (15.0)	0 (0.0)	−20.6–6.3	1.000

Adverse effects in number of events and percentage for both groups during the 6-month follow-up. Fisher's exact test was used for statistical comparisons, 95% confidence intervals (CI) were calculated using the Wald method and $p < 0.05$ was set as significant.

indicating that repeated exposures to tests alone did not guarantee maintenance of higher scores. Additionally, we had very few non-white participants. Still, the major limitation of this trial was the sample sizing, in part explained by it being conducted between 2020 and 2021, during the COVID-19 pandemic and before vaccination commencement. Only 29 patients were randomized and 28 actually completed the trial; these challenging circumstances hindered our ability to achieve the ideal sample size (37), as initially calculated. Therefore, we cannot rule out the sample size effects on the lack of statistical power neither for adverse events or secondary outcomes, in both cases, no statistical differences between the placebo and cannabis groups were achieved. As stated in trial procedures, baseline values for primary outcome (MMSE) and age but not secondary outcomes were included in the patient randomization process, which could have interfered in slightly diverse baseline values, for instance in terms of ADAS-Cog, CSDD, ESS, and NPI-Q scores. The overall fluctuations in these scores from baseline to trial endpoint could indeed also be explained by small sample size, but at least in part, also by individual variables, placebo effect, and/or tolerance to treatment effect. Consequently, we cannot entirely dismiss the possibility that the treatment might exert effects on adverse events or secondary outcomes, such as cannabis-associated increased appetite and weight gain or AD-associated sleep and quality of life alterations. However, given the framework of our experimental trial and the baseline profiles of our patients, such effects remained overlooked.

Considering available data, this is the longest clinical trial evaluating cannabinoids effects on AD-associated dementia. Data from all clinical trials currently published verse on the effects of exogenous cannabinoids treatment, in the order of milligrams, mostly for agitation in dementia, AD-related or not.[4,23,24] Results from the latest multicenter study sponsored by Johns Hopkins University, which was completed last May, are yet to be published.[25] In light of AD being a chronic disease, 6 months is a reasonable timeframe to observe changes in symptoms due to treatment. Current AD treatments are basically anticholinesterase drugs and memantine, an NMDA receptor blocker; both exhibiting limitations and poor effectiveness.[26] The FDA already approved three Aβ antibodies to treat AD, Aducanumab, Lecanemab and Donanemab. Aducanamab binds to Aβ aggregated forms, such as soluble oligomers and insoluble fibrils,[27] Lecanemab binds soluble Aβ protofibrils with high affinity and insoluble fibrils,[28] and Donanemab binds mostly insoluble fibrils.[29,30] All drugs substantially reduce Aβ burden. However, important adverse events have been reported while clinical results were notably modest and hence, subject to controversy.[27]

In the case of Aducanumab, the antibody was recently withdrawn from the market.[30] Conversely, in this trial, the cannabis extract demonstrated its safety and clinical effectiveness at very low doses. In other words, cannabis treatment could be a safe and affordable treatment to a much larger number of patients in comparison to the recently FDA-approved antibodies, and this should be considered advantageous of this treatment type, which still retains illegal status in multiple locations and is typically regarded as "alternative". In our preliminary experience,[12] higher cannabinoids dosage does not improve cognitive performance while could possibly yield undesired notorious psychoactive side effects (e.g., euphoria, paranoia, anxiety, and hallucinations), yet it would be valuable to substantiate or contradict these findings with larger studies. Other studies with different cannabinoid ratios could also represent an advance in understanding beneficial effects of CBD and THC, alone and combined, and shed light to possible therapeutic mechanisms of the endocannabinoid system tuning on AD.

Several studies have demonstrated deleterious changes in the endocannabinoid system of AD animal models and patients.[31–33] *In vitro* and *in vivo* studies have shown the potential of cannabinoids, THC and CBD, as therapeutics for AD.[5,33–37] THC acts as agonist on both CB1R and CB2R cannabinoid receptors, with a higher affinity for CB1R, while CBD predominant site of action is still debatable. Noteworthy, both molecules act as well on non-cannabinoid receptors. The former is shown to interact with different members of the TRP (Transient Receptor Potential) family (such as vanniloid, ankyrin, and melatonin), while the latter has been demonstrated to interact with certain members of the serotoninergic and adrenergic receptors.[38,39] On one hand, CBD most probably activating microglial CB2R has ameliorated inflammation, Aβ burden, and memory deficits in AD transgenic mouse models, as well as attenuated neuronal death and induced neurogenesis via peroxisome proliferator-activated receptor-γ (PPARγ), in rats submitted to Aβ administration.[5,40,41] On the other hand, just as synthetic agonists-induced CB1R activation mitigated Aβ-induced tau hyperphosphorylation via astroglial NO inhibition *in vitro,*[34] THC-induced CB1R activation promoted BDNF-driven neurogenesis, leading to cognitive improvement in aged mice.[36] Recently, it has been demonstrated that in old mice chronic low-dose THC improved spine stability resulting in a long-lasting increase in spine density.[42] Furthermore, the anti-inflammatory, neuroprotective, and antioxidant actions of cannabinoids may assist in AD treatment.[43] Considering that AD appears to be influenced by multifactorial mechanisms, such as Aβ accumulation, tau hyperphosphorylation, inflammation, gliosis, oxidative stress, neuronal death,[2,43] and that the endocannabinoid system and cannabinoids can modulate all these mechanisms,[31,33–37,44] the idea of cannabis effect being multi-targeted is strongly supported. Therefore, clinical cognitive improvement observed in our patients could be a cumulative result of CB2R-mediated cannabinoid actions mostly in glial cells and/or the CB1R-mediated cannabinoid effects in neuronal cells, or still the combination of them, which could be instigating direct impact on cognitive performance, or indirect by possibly improving secondary symptoms. Note, we are not ruling out possible beneficial cannabinoid effects mediated by non-cannabinoid receptors as TRP channels, for instance, recently linked to AD.[45] Although Aβ buildup is the main pathological marker for AD, neuroinflammation and oxidative stress seem to be the missing puzzle piece in between the classical hallmarks and neuronal death.[46] This might explain why some Aβ-targeted drugs or -antibodies designed to treat AD had disappointed or completely failed in clinical trials despite their preclinical promising results.[27,28,47,48] Thus, using a drug that could target and ameliorate not only the Aβ burden but also the majority of associated mechanisms, as cannabis has shown to do, could represent a more efficient strategy to treat AD than using a single-targeted drug or antibody. Until fully proven, conceivably even the association of cannabinoids with other therapeutic strategies could elicit a cascade of beneficial effects enhancing AD patients' care.

In this trial, we report the administration of very low doses of cannabis extract to AD patients, resulting in significant alleviated cognitive loss over a 6-month follow-up period compared to the placebo group. These findings are preliminary but instrumental in opening a promising avenue for the use of cannabinoids as a potential therapeutic option for AD dementia. Nevertheless, longer and larger multicenter phase II, and hopefully phase III trials, are necessary to further establish the efficacy and safety of cannabis as a therapy for AD and, perhaps, other types of dementia.

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Ethical considerations

This trial is in accordance with the previously approved ethical protocol (CAEE 098 13219.9.0000.0107, CEP Unioeste, Brazil) and followed international ethical guidelines, including but not limited to Declaration of Helsinki and International Conference on Harmonization E6 Good Clinical Practice Guidelines. This trial also followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Consent to participate

All participants/caregivers provided written informed consent to participate in this trial, according to approved ethical protocol. This trial was officially registered in the Brazilian platform ReBEC (Rede Brasileira de Ensaios Clínicos; # U1111-1258-2058). The Trial Protocol and Statistical Analysis Plan are available as Supplemental Material.

Consent for publication

All participants and/or their caregivers provided written informed consent for the publication of the trial results, in an article or thesis format.

Author contribution(s)

Rafael de Morais Cury: Conceptualization; Data curation; Investigation; Methodology; Validation.
Taynara da Silva: Investigation; Writing – original draft.
Fernando Cezar-dos-Santos: Data curation; Formal analysis; Software; Writing – original draft.
Yasmin Rafaela Correia Fakih: Investigation.
Karlin Andrea Ramírez Narvaez: Investigation.
Murilo Chaves Gouvea: Methodology.
Carlos Espínola: Methodology.
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The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FPN and FAP are partners in a contract research organization focused on cannabis clinical trials. The remaining authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statement

All data from this trial are publicly available in the Mendeley Repository (https://data.mendeley.com/datasets/j5xdt8fd3 s/4) under the DOI number 10.17632/j5xdt8fd3s.4.

Supplemental material

Supplemental material for this article is available online.

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