Oral Thc: Cbd Cannabis Extract in Main Symptoms of Alzheimer Disease: Agitation and Weight Loss

Beniamino Palmieri
University of Modena and Reggio Emilia
Maria Vadalà MsC (mary.vadala@gmail.com)
University of Modena and Reggio Emilia

Research Article

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Abstract

OBJECTIVES: Ten million new cases of dementia are recorded annually worldwide, with agitation and idiopathic weight loss being the most common symptoms. Several pharmacological therapies have emerged in recent years, but the clinical use of cannabis extracts in older patients with AD is constantly growing. This retrospective, analytical, observational, spontaneous trial aimed to enhance the clinical action of THC: CBD cannabis extract administration in AD patients with severe symptoms such as agitation, weight loss, cognitive impairment, and sleep disturbance.

METHODS: Thirty patients (9 men and 21 women) diagnosed with mild, moderate, or severe AD, aged 65-90 years, appealing to our Second Opinion Medical Consultation (Modena, Italy), were enrolled and required to use oil-diluted cannabis extract, Bedrocan® (22% THC, 0.5% CBD, Olive Oil 50 ml), twice a day for 12 weeks. The efficacy of cannabinoid therapy was evaluated at baseline and 12 weeks after therapy, employing three self-administered questionnaires completed by the parents of the enrolled patients: NPI-Q, CMAI, and MMSE.

KEY FINDINGS: The NPI-Q demonstrated a reduction ($p<0.0001$) in agitation, apathy, irritability, sleep disturbances, and eating disturbances, consequently improving caregiver distress. Levels of physically and verbally aggressive behaviours, measured using the CMAI questionnaire, were lower ($p<0.0001$) in all patients. The MMSSE questionnaire confirmed a significant decrease ($p<0.0001$) in cognitive impairment in 45% of the patients.

CONCLUSION: Our anecdotical, spontaneous, and observational study demonstrated the efficacy and safety of oil-diluted cannabis extract in patients with AD. The limitations of our study are: 1) small patient cohort, 2) absence of control group, 3) self-administered questionnaires that are the most practical but not objective instruments to assess the neurologic functions of AD patients.

1. Introduction

In 2019, 36 million people worldwide were affected by dementia, accounting actually for 60–80% of AD cases (1, 2). This number, owing to demographic changes and population aging, could reach 115 million by 2050 (3). In 1906, the German psychiatrist and pathologist Alois described Alzheimer's disease as a neurodegenerative disorder, distinguished by declined cognitive memory, language, and perceptual-motor abilities that have a negative effect on daily living activities (4, 5). Behavioural and psychological changes such as apathy, disinhibition, anxiety, insomnia, and hallucinations, caused mainly by inflammation, oxidative stress, and impaired function of degradation pathways, are frequently added (6–8). The most common symptoms were agitation and idiopathic weight loss. Agitation usually affects 20% of AD cases, increasing to 50% after admission to long-term care facilities. It definitely worsens the life quality requiring more accurate surveillance and a greater institutionalization rate (9, 10). Weight loss is confirmed in one-third of patients, it involves an increased risk of falls and worsens rapid cognitive decline (11–13). AD can also be classified into two types: 1) sporadic AD, which dominates in > 95% of

patients, and 2) familial early onset form (FAD), which is determined mainly by mutations of genes encoding β-amyloid precursor protein (APP) and presenilin-1 and − 2 (PS1 and PS2) and is evidenced in < 5% of cases (14, 15). Both forms of AD are histologically characterized by dysfunctional deposition of β-amyloid protein (Aβ) (Ab1-42 and Ab1-40) in extracellular senile plaques in different brain zones, including the hippocampus, cerebral prefrontal cortex, and amygdala, and by tau hyperphosphorylation in major brain zones involved in memory and cognition (16–21).

The main therapeutic approach makes acetylcholine available by inhibiting acetylcholinesterase (22).

The degeneration of acetylcholine determines cholinergic deficits in AD patients, particularly in the hippocampus and neocortex (23). The main acetylcholinesterase inhibitors are donepezil, galantamine, and rivastigmine, which inhibit both AChE and butyrylcholinesterase. Nevertheless, several clinical trials with a placebo group, based on common pharmacological AD treatments with cholinesterase inhibitors, showed that these inhibitors are efficient mostly for mild-to-moderate AD stage but not in severe stage (24).

The cannabis plant (*Cannabis sativa* L.), including cannabidiol (CBD) and Δ-9-tetrahydrocannabinol (THC), has been constantly growing in older people with AD (25, 26). These components show neuroprotective action against excitotoxicity and acute brain damage by activating two main cannabinoid G-protein coupled receptors, CB1 and CB2 (21, 27–30). In fact, CB1 receptors appear in glial cells and neurons and modulate excitatory and inhibitory neurotransmission (31). Furthermore, CB1 plays a protective role against excitotoxicity and the induction of repair mechanisms in response to neuronal damage (32, 33). Indeed, stimulation of CB1 receptors reduces the neurotoxic effect of Aβ (34–36) and regression of Aβ-induced memory impairment (37–39).

The antioxidant neuroprotective action of CBD in neurodegenerative diseases counteracts Ab plaque formation and neurofibrillary tangles *in vivo* and reduces ROS and lipid peroxidation (25). Esposito et al. (40) highlighted the anti-inflammatory action due to reduced levels of inducible nitric oxide synthase (iNOS) and interleukin 1 beta (IL-1b). It also prevents apoptosis by upregulating pro-caspase 3 levels and at the same time downregulating caspase 3 levels in Ab-stimulated PC12 neurons (40). Subsequently, the same authors showed that its mechanism of action seemed to be selectively mediated via peroxisome proliferator activated receptor gamma (PPARg) (41). Eubanks et al. (42) demonstrated the clinical role of exogenous THC as a novel AD drug candidate. They discovered that THC could prevent acetylcholinesterase-induced Aβ aggregation by means of enzymes in a crucial zone affecting amyloid production (42). In a preclinical study, it was shown that very small doses of THC could slow down the production of β-amyloid proteins and enhance mitochondrial function, suggesting a therapeutic option for the progression of disease (43).

In 1997, 15 patients with dementia who refused nutrition were treated with cannabis product (2,5 mg THC twice daily) for 42 days (44). The results showed reduced Cohen-Mansfield Agitation Inventory (CMAI) scores and upgraded negative affect scores. In 2006, Walther et al. (45) assessed the effect of dronabinol (2,5 mg daily, at 19.00h, for 14 days) on sleep and behavioral disturbances in 5 AD patients with AD.

Actigraphy and Neuropsychiatric Inventory (NPI) scores confirmed a significant improvement in agitation, appetite, and irritability, compared to baseline, with no side effects (45). Hospitalized AD patients were treated sporadically with various cannabis compounds: THC (2.5–30 mg/dose) and/or CBD, disclosing marked benefits on neuroleptic drug sparing, reduced agitation, increased appetite, sleep quality, and nursing care demands (46). Aso and coworkers evaluated also the therapeutic properties of oromucosal spray, Sativex® (2,7 mg THC/2,5 mg CBD in 100 ml) in AbPP/PS1 mice with late-onset AD (47). Intraperitoneal administration (0.75 mg/kg each for 35 days) reduced cognitive impairment and levels of soluble Ab1–42 but not those of Ab1–40 (47). It supposes that matched therapy may be more efficacious than treatment with either cannabis component alone. Woodward et al. (48) analyzed the outcomes of dronabinol therapy (7 mg/day for 7 weeks) in 13 patients with AD with behavioral or appetite disturbances. Cannabis administration enhanced scores on the Pittsburgh Agitation Scale (PAS) and Clinical Global Impression (CGI), and also improved sleep time and percentage of food consumed during the therapy (48). Herrmann et al. reported the therapeutic effect (1–2 mg daily for 6 weeks) of a synthetic THC analog, nabilone, in 39 AD patients with agitation (49). The author observed an improvement in the Cohen-Mansfield Agitation Inventory (CMAI) with a moderate effect size and similar improvements in the Posttraumatic Adjustment Scale (PAS) and Clinical Global Impression (CGI).

Therefore, the described studies suggest that oral cannabis products have therapeutic effects on patients with AD.

The aim of our retrospective, anecdotical, observational, spontaneous trial was to enhance clinical action of oral THC:CBD cannabis extract administration in AD patients with severe symptoms, such as agitation, weight loss, cognitive impairment, sleep disturbance etc., and its adverse effects. In particular, the objective of this study was to investigate the therapeutic action of this oral cannabis extract in AD patients for at least 3 months. We specifically examined: -The efficacy of oral cannabis extract in agitation, -The efficacy of oral cannabis extract in sleep disturbance, -The efficacy of oral cannabis extract in cognitive impairment, and -Potential occurrence of adverse effects.

2. Materials And Methods

The study was approved by the local ethics committee Second Opinion Local Institutional Review Board (IRB) and conducted in accordance with the ethical standards of the Declaration of Helsinki.

Patients. Thirty patients (9 men and 21 women) diagnosed with mild, moderate, or severe Alzheimer disease, aged 65–90 years, directed to our Second Opinion Medical Consulting, from February 2018-January to 2020, accompanied by their respective caregivers, were included in this investigation **(Table 1)**. The Second Opinion Medical Network is a consultation referral web and medical office system enclosing a wide panel of specialists, to whom any patient with any illness or syndrome that is not adequately satisfied by the diagnosis or therapy can be applied for an individual clinical audit (50–53).

The main symptoms of the enrolled patients were agitation, appetite loss with consequent weight loss, sleep disturbances, and cognitive impairment.

Inclusion and exclusion criteria. The inclusion criteria were as follows: mild/moderate/severe AD symptoms for at least 24 weeks and seeking adequate therapy; behavioral disorders (Neuropsychiatric Inventory [NPI-Q] score > 2), agitation (Cohen-Mansfield Agitation Inventory [CMAI] score > 4), and cognitive impairment (Mini Mental State Examination [MMSE] score < 10). The exclusion criteria were the presence of severe cardiac insufficiency, unstable heart rhythm, orthostatic hypotension, antidepressant and anxiolytic therapy, and a history of psychotic disorder.

The patients were required to undergo cannabis oil extract sublingually, twice daily for 12 weeks.

The specific personnel of the Second Opinion Medical Consulting Network evaluated monthly tolerability and side effects, such as hypertension, tachycardia through mail, telephone, WhatsApp, Skype, or visit if required.

The efficacy of cannabinoid therapy was evaluated at baseline and 3 months after therapy using three self-administered questionnaires completed by the parents of enrolled patients: NPI-Q, CMAI, and MMSE. The first determines the severity of 12 neuropsychiatric symptoms, such as hallucinations, agitation, depression, anxiety, euphoria, apathy, irritability, aberrant motor behaviors, nighttime behavioral and appetite/eating disorders, and caregiver upset. The severity scale ranges from to 1–3 points (1 = mild, 2 = moderate, and 3 = severe), while the scale for evaluating caregiver distress has scores ranging from to 0–5 (0 = no distress, 1 = minimal distress, 2 = mild distress, 3 = moderate distress, 4 = severe distress, and 5 = extreme distress) (54). The CMAI determines the frequency of agitated behaviors and consists of 29 items typically associated with agitation, including physically aggressive (e.g., hitting, pushing, kicking, cursing), and non-aggressive actions (e.g., pacing, inappropriate dressing or undressing), verbally aggressive (swearing), and non-aggressive habits (uncooperative, constant request for attention), measured before a 14-days period on a 7-point scale (0 = never occurred, 1 = less than once a week, 2 = once or twice a week, 3 = several times a week, 4 = once or twice a day, 5 = several times a day, 6 = several times an hour) (55–57). In conclusion, the MMSE is the main instrument used to screen for cognitive impairment in patients with AD, considering several domains of cognitive function such as time and place orientation, concentration, naming familiar items, repeating a common expression, and reading/writing a sentence. Lower score of scale indicates significant impairment (30 – 26 = normal, 20–25: mild, 10–19: moderate, 0–9:severe) (58, 59).

Pharmacological Interventions. The full cannabis plant extract, Bedrocan®, is obtained from Bedrocan International BV (Veendam, The Netherlands) and the oil-diluted cannabis extract is prepared by the galenical Pharmacy Dr. Ternelli (Bibbiano, Reggio Emilia, Italy). Bedrocan® that contains 22% THC (220 mg/g) and 0,5% CBD (5mg/g), is prepared from standardized cannabis plant material (Cannabis flos) by means of Romano-Hazekamp or Sifap-Sifo extraction and diluted in oil (1 g of cannabis in 10 g of olive oil). The dosage usually begins with low dose (15 drops) and titrates upwards to the recommended maximum dose of 1 ml/day (30 drops) followed by a reduction down to 0.5 ml/day at month 3 **(Table 2)**.

No medical treatment was administered in combination with chemotherapy. The patients in the treatment with quetiapine fumarate 0.25 mg for sleep disturbance (n = 3) stopped the drug one week before the oil-

diluted cannabis extract therapy.

Statistical analysis. Statistical analyses were performed using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA). The data were analyzed using an unpaired t-test with Welch's correction. $p < 0.05$ was considered significant.

3. Results

All enrolled patients completed the cannabis treatment for three months. None of the patients complained of mild, moderate, or severe adverse effects. The NPI-Q questionnaire showed a significant reduction ($p < 0.0001$) in typical behavioral problems, particularly significative decrease of agitation, apathy, irritability, sleep disturbance, and eating disturbances, consequently improving caregiver distress (Fig. 1). Levels of physically and verbally aggressive behaviors, measured using the CMAI questionnaire, were lower ($p < 0.0001$) in all clinical cases (Fig. 2). Some 'performing repetitive behaviors', such as repeating a question or an action, tapping fingers, were observed more commonly. The MMSSE questionnaire confirmed severe cognitive impairment (score < 10) before cannabis treatment, which was reduced to mild/moderate (score:15–17) in 45% of the patients. The majority (70%) of the clinical cases showed an increase in appetite, probably due to the known effects of CB1 agonism (Fig. 3).

However, caregiver feedback (son/daughter, wife/husband, brother/sister) about the treatment was extremely positive overall. They reported definite improvement in daily behavior: the patient appeared quieter, less excitable and irritable, more adherent to environmental situations, and even more properly laughing and smiling.

At the end of cannabis treatment, the patients significantly reduced their behavioral disorders, including screaming, tearing clothes, and claiming for common daily living activities, such as washing, dressing, climbing stairs, and eating alone. One woman (88 years old) with persistent agitation stopped therapy after 30 days.

4. Discussion

Despite the many confirmatory experimental researchers, the clinical evidence of the effectiveness of cannabinoids (CBD and/or THC) in AD has not been confirmed statistically, because of the small sample size of the treated patient groups and some bias in the homogenous meta-analysis of individual studies.

Many neurophysiological investigations have shown that high THC concentrations inhibit cholinergic transmission in the limbic system and cortex, impairing memory and cognition; however, the side effects observed after THC-based therapy are similar to those observed after cholinergic antagonists, such as 4-DAMP, cyclizine, gallamine, and methdilazine, as studied by Varvel et al. (60).

Cao et al. (43) examined the toxicity of THC in N2a-variant amyloid-β protein precursor (AβPP) cells incubated with a low dose of compound (100 µL in 2× concentrations for each well = 2.5 nM) and

confirmed that this compound could reduce the synthesis of the AD pathological marker, slowing down or stopping the progression of the disease.

Similar results were observed in old mice (12–18 months) with cognitive symptoms (memory deficit and increased learning capacity) treated with a low dose of THC (61). The improved cognitive functions, with consequently improved expression of synaptic marker proteins and hippocampal spine density, were similar to those of untreated mice with the same symptoms, according to other studies (47, 62–64).

In our observational and spontaneous study, we chose cannabis oil because it can be administered in different food options (bread, breadstick, crackers, etc.), compared with an oral spray that is poorly adsorbed in elderly patients, or cannabis tincture (alcoholic), responsible for mucositis or oral ulcers (65).

This treatment reduced behavioral misconduct, such as agitation and cognitive impairment, probably because of the direct effect of cannabis on Aβ processing, which could increase the level of available acetylcholine and anticipate acetylcholinesterase-induced Aβ aggregation.

During the treatment period, we observed an increased quality of life for each patient, and consequently, a decrease in caregiver burden and costs of medical care and assistance.

Conclusion

Our analytical, spontaneous, and observational study demonstrated the efficacy and safety of THC:CBD cannabis extract in patients with AD.

The main limitation of our study was the small clinically cohort of patients. Given the small size of the patient sample, we cannot exclude error rates (Type 1 and Type 2 errors) and cannot ensure that our results may be replicated in future research with larger sample size. Considering the low size of our patient sample and related low statistical power, our study should be viewed as an anecdotal one and to help as an input for larger studies. Other limitations of our study are as follows: 1) the absence of a control group, and 2) self-administered questionnaires that are the most practical but not objective instruments to assess the neurologic functions of AD patients.

In conclusion, the lack of clinical studies in this area validates further trials, particularly randomized controlled studies, to assess the pharmacokinetics and pharmacodynamics of cannabis treatment in different clusters of AD symptoms.

Declarations

FUNDING

Funding information was not applicable/no funding was received.

CONFLICTS OF INTEREST

The Authors declare that there is no conflict of interest

DATA TRANSPARENCY

The authors affirm that this manuscript is an honest, accurate, and transparent account of this study. being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained

DATA AVAILABILITY

The authors declare that data supporting the findings of this study are available in the article.

ETHICS APPROVAL

Approval was obtained from the local ethics committee Second Opinion Local Institutional Review Board (IRB), named: Second Opinion Medical Network, the number of Approval is 7/2021

AUTHORS CONTRIBUTION

The authors confirm their contribution to the paper as follows: study conception and design: MV; data Collection and writing BP,

CONSENT TO PARTECIPATE

The participants consented to the submission of the case report to the journal. Each Patient signed Informed consent regarding publishing his data and photographs" statement in the ethics approval and consent to participate section.

CONSENT FOR PUBLICATION

Each patient gave its consent for the publication of identifiable details, which can include photographs and/or case history and/or details within the text (“methods, results”) to be published in the above Journal

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All methods were performed in accordance with the relevant guidelines and regulations, according to a statement in the ethics approval and consent to participate.

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Tables

Tables 1 and 2 are not available with this version

Figures

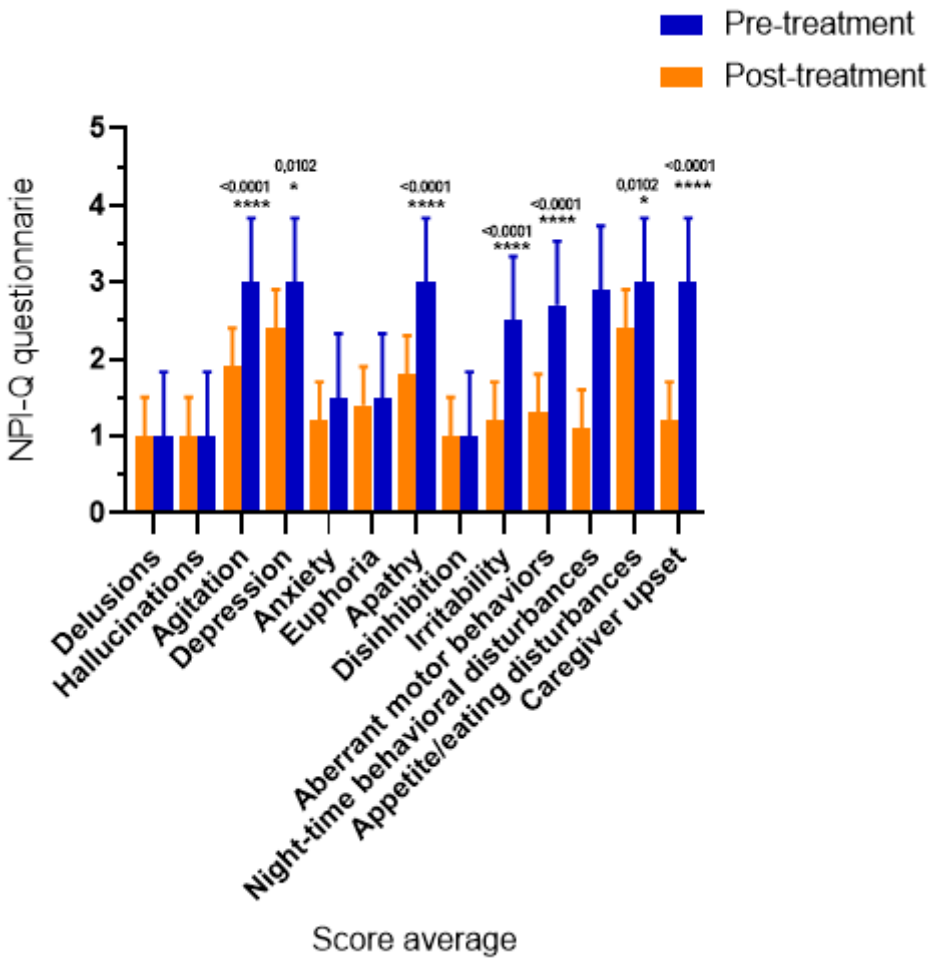

Figure 1

Graphical representation of NPI-Q questionnaire before and after treatment. The bar graph shows the results of NPI-Q text before (blue colour) and after (orange colour) treatment with oil-diluted cannabis extract. Data are presented as the mean ± standard deviation (SD). There were significant differences between pre- and post-treatment. ****P<0.0001 pre vs. post-treatment

Figure 2

Graphical representation of CMAI questionnaire before and after treatment. Bar graphs showing the CMAI questionnaire results for the pretreatment (fuchsia bar) and posttreatment (green bar) group. Data are presented as the mean ± standard deviation (SD).

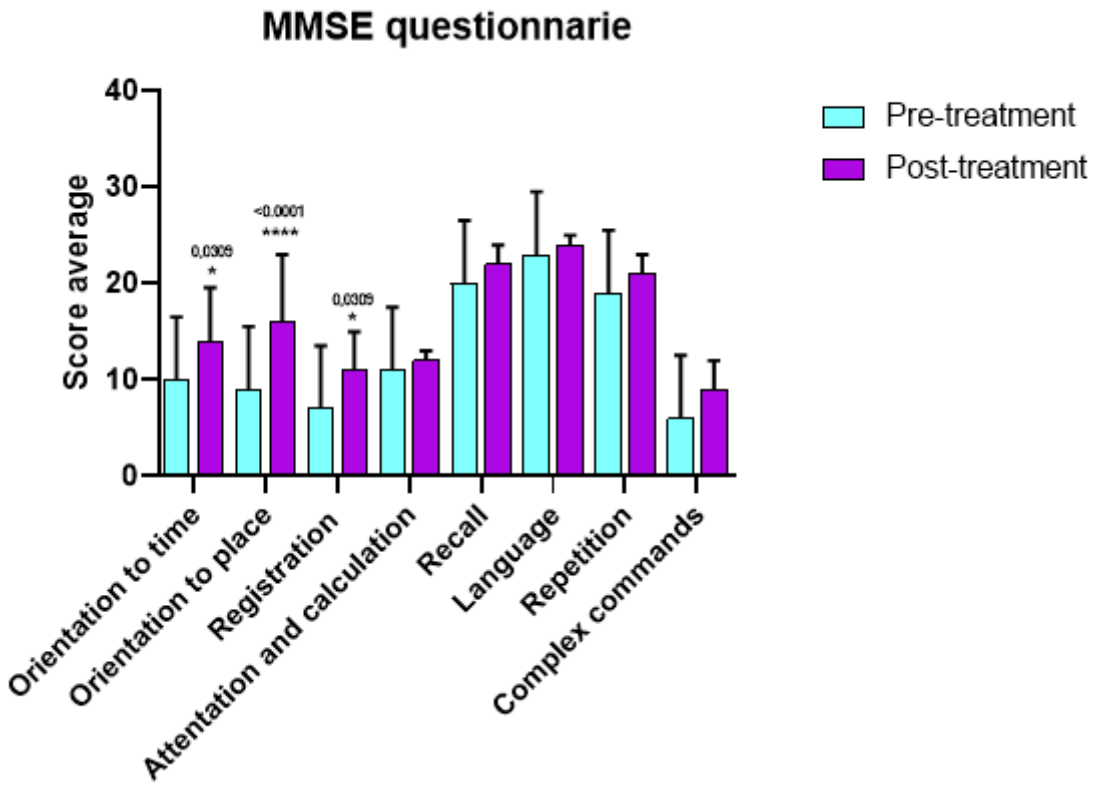

Figure 3

Graphical representation of MMSE questionnaire before and after treatment. Data are presented as the mean ± standard deviation (SD). Differences in symptoms such as orientation to time or to place and registration were considered statistically significant relative to the pre-treatment group. ****P<0.0001 pre vs. post-treatment