SUPPLEMENTARY MATERIAL

Cannabidiol for behaviour symptoms in Alzheimer's disease (CANBiS-AD): A randomised, double-blind, placebo-controlled trial

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METHODS

CANBiS-AD (Cannabidiol for behaviour symptoms in Alzheimer's disease) was a phase 2a, parallel-group, double-blind, placebo controlled, randomised trial. The participants were randomly assigned (1:1) to receive either CBD or placebo, together with treatment as usual, which was computer generated. Participants, carers, researchers and study sponsors were all blind to the treatment assignment until data unblinding done following database lock.

During the double-blind treatment period, study visits were done at baseline and days 8, 15 and 43, with weekly telephone interviews for compliance and safety check. A final follow-up for safety was done following 4 weeks after the last dose of study medication. All visits took place either in the patient's place of residence, or at local Clinical Research Facility centre.

The primary outcomes of this feasibility study were estimation of recruitment, treatment compliance and retention rates. Secondary outcomes were changes in 6 weeks from baseline in behaviour symptoms assessed NPI-C [10] and Cohen Mansfield Agitation Inventory-short form, CMAI-SF [11]; cognition by Standardised Mini-Mental State Examination (SMMSE) [12], Addenbrooke's Cognitive Examination-III (ACE-III) [13] and Hopkins Verbal Learning Test (HVLT) [14]; daily activities on the Bristol Activities of Daily Living Scale (BADLS) [15] and quality of life using Dementia Quailty of Life measure (DEMQOL) and DEMQOL-Proxy [16]. Clinical Global Impression of Change (CGIC) [17] was used to evaluate global change associated with treatment.

Safety outcomes, measured over 6 weeks, included self-reported adverse events, adverse events leading to medication/study discontinuations, serious adverse events, mortality, and assessment using Columbia Suicide Severity Rating Scale, physical examinations, vital signs (heart rate and blood pressure), physical examination and electrocardiogram (ECG)- 12 lead ECG obtained at baseline, day 15, and day 43). Clinical laboratory tests were done during these visits for haematology, clinical chemistry, glucose, liver function test, lipid profile and thyroid function tests.

RESULTS

Adverse events, severe adverse events and deaths were ascertained from screening to 6 weeks of treatment period and then for 4 weeks after last dose of treatment. A total of 34 AEs were observed during the entire period of the study from all causes in both groups. In total, 4 (27%) of the 15 patients experienced at least one treatment emergent adverse event (TEAE)- 'Possibly' or 'Likely' related [TEAE]. Of the eight AEs 'likely related ' TEAEs to be due to study medication, all were observed in the CBD group and were dizziness (n=4), increased alkaline phosphatase (n=1), increased gamma-glutamyl transferase (n=1) and somnolence (n=2). 2 (13%) patients experienced TEAEs that were assessed as 'likely related'. All the

dizziness episodes and somnolence were experienced by one patient and another patient had the raised liver enzymes. They were mild in intensity and resolved without intervention. The one serious AE (SAE) was a fall which was experienced by one of a participant in the placebo group and after the 6 weeks treatment period. There were no deaths reported in either group during the trial.
No notable differences were observed for physical examination, vital signs, body weight, ECG or clinical laboratory tests in both the treatment groups. There were no changes on the Columbia Suicide Severity Rating Scale for patients in both arms.

On the CGIC all the 7 patients in the placebo group showed 'No change' and 6 of 8 patients in the CBD group showed 'No change' with one each for 'Moderate improvement' and 'Marked improvement' after 6 weeks of treatment.

Table 1 – Baseline information for sociodemographic and cognitive variables between groups on placebo and cannabidiol

	Placebo (n = 7)	**Cannabidiol (n = 8)**
Age	78.51 (±8.69)	75.60 (±6.68)
Gender	Female (100%)	Female (88%)
Marital status		
Married	5 (71%)	5 (62.5%)
Widowed	2 (29%)	1 (12.5%)
Divorced	0 (0%)	2 (25%)
Accommodation		
Living alone	1 (14%)	1 (12.5%)
Living with spouse/cohabiting	5 (71%)	4 (50%)
Living with family	1 (14%)	3 (37.5)
Ethnicity		
White	6 (86%)	7 (87.5%)
South Asian	0	0
Black-Afro Caribbean	1 (14%)	1 (12.5%)
Duration of diagnosis at presentation (in months)	21.57 (±18.95)	32.88 (±32.72)
Education in years	12.57 (±3.21)	12.50 (±2.20)
Medications		
Antidementia	5 (71%)	6 (75%)
Antidepressant	3 (43%)	5 (62.5%)
Antipsychotic	1 (14%)	0
sMMSE	15.6 (±9.6)	15.6 (±9.5)
Total ACE III	37.6 (±26.5)	37.3 (±27.8)
NPI-C (Anxiety)	7.4 (±6.1)	7.8 (±6.8)
NPI-C (Agitation)	11.7 (±6.3)	12.6 (±6.7)
NPI-C (Hallucinations)	1.9 (±3.3)	3.1 (±5.4)
NPI-C (Delusions)	7.1 (±4.0)	2.4 (±3.1)
NPI-C (Total)	83.29 (±41.70)	78.12 (±42.99)
CMAI-SF total	28.9 (±8.4)	28.3 (±7.4)

BADL	25 (±14)	25 (±12)
DEMQOL	101 (±7)	86 (±11)
DEMQOL Proxy	85 (±15)	84 (±19)

Values are mean (±SD) and %. sMMSE, Standardised Mini-Mental State Examination; NPI-C, Neuropsychiatric Inventory-Clinician Impression; CMAI-SF, Cohen Mansfield Agitation Inventory-short form; ACE-III, Addenbrooke's Cognitive Examination-III; HVLT, Hopkins Verbal Learning Test; BADLS, Bristol Activities of Daily Living Scale; and DEMQOL and DEMQOL-Proxy Dementia Quailty of Life measure. P value

Table 2: Summary of adverse events for patients from baseline to week 10 for who received placebo and cannabidiol treatment

MedDRA* high-level grouping	Individual AEs	All patients (n=15)	Placebo (n=7)	Cannabidiol(n=8)
Gastrointestinal disorders	Nausea	3	2	1
	Per rectal bleed	1	0	1
Nervous System disorders	Dizziness/Light-headedness	5	0	5
	Headache	1	1	0
Psychiatric disorders	Somnolence/Drowsiness	2	0	2
	Acute stress reaction	1	1	0
	Anxiety/Depression	1	0	1
Infections and infestations	Infection, unspecified (Covid-19)	3	2	1
	Urinary tract infection	2	2	0
	Respiratory tract infection (cold, cough)	2	1	1
	Cellulitis-left leg	1	1	0
General disorders and administration site conditions	Pain, non-specific, stomach-ache (covid-19 symptom)	1	0	1
	Fatigue (lethargy)	1	1	0
Blood and Lymphatic System disorders	Swelling of hands and ankles	1	1	0
Injury, poisoning and procedural complications	Fall	5	3	2
Investigations	Raised Gamma GT	1	0	1
	Raised alkaline phosphatase	1	0	1
Skin and subcutaneous tissue disorders	Rash	1	0	1
	Necrotic excoriation (blackened elbows)	1	0	1

Medical Dictionary for Regulatory Activities (MedDRA) is the standardised international medical terminology used by regulatory authorities when reporting adverse events

Table 3 – Mean differences in change from baseline to end of week 6 treatment.

	Placebo (n=7)	CBD (n=8)
ACE-III Attention	-0.7 ± 1.7	-0.9 ± 2.3
ACE-III Fluency	-0.3 ± 1.0	-1.9 ± 2.1
ACE-III Language	-2.0 ± 4.3	0.7 ± 2.4
ACE-III Visuospatial abilities	-1.2 ± 1.9	-0.1 ± 3.7
ACE-III Memory	-0.2 ± 2.6	1.4 ± 3.2
ACE-III Total	-4.0 ± 6.5	-0.7 ± 11.0
sMMSE	-1.2 ± 2.7	-1.6 ± 3.3
HLVT Part A	-0.5 ± 4.1	1.0 ± 2.6
HLVT Part B	-0.3 ± 2.5	1.1 ± 2.9
HLVT Part C	-0.5 ± 1.7	0.0 ± 1.9
DEMQOL	3 ± 6	5 ± 6
DEMQOL - Proxy	1 ± 19	7 ± 15
BADLS	3 ± 6	-2 ± 6
CMAI Aggressive Behaviour	0.1 ± 2.0	-1.3 ± 3.2
CMAI non-aggressive Behaviour	0.9 ± 1.8	-0.9 ± 2.7
CMAI Verbally Agitated Behaviour	-0.5 ± 2.9	-3.1 ± 3.6
CMAI Total	0.2 ± 4.8	-5.3 ± 8.2
NPI-C* Clinician Impression		
NPI-C* total	-10.14 ± 38.15	-29.86 ± 51.50
NPI-C* delusions	-3.4 ± 3.1	-1.5 ± 2.8
NPI-C* hallucinations	-1.0 ± 3.1	-2.6 ± 4.8
NPI-C* agitation	-0.9 ± 4.9	-3.5 ± 6.0
NPI-C* anxiety	-1.0 ± 6.8	-4.9 ± 6.9
NPI-C* aggression	-1.1 ± 3.0	0.4 ± 2.2
NPI-C* dysphoria	-2.6 ± 5.5	-2.9 ± 7.7
NPI-C* elation / euphoria	-0.3 ± 0.5	-0.1 ± 2.2
NPI-C* apathy /indifference	1.6 ± 10.3	-6.5 ± 11.2
NPI-C* disinhibition	0.3 ± 5.6	0.6 ± 6.3
NPI-C* irritability /lability	4.3 ± 3.0	3.4 ± 4.8
NPI-C* aberrant motor disturbance	-0.6 ± 2.2	0.3 ± 2.3
NPI-C* sleep disorders	-3.1 ± 2.9	-0.6 ± 2.7
NPI-C* appetite and eating disorders	-0.9 ± 1.2	-2.1 ± 3.1
NPI-C* aberrant motor vocalizations	1.0 ± 4.3	-0.8 ± 4.0
NPI-C carers distress**		
NPI-C** delusions	-3.6 ± 5.5	-0.8 ± 4.0
NPI-C** hallucinations	-2.9 ± 6.0	-3.0 ± 9.9
NPI-C** agitation	-4.4 ± 11.7	-4.8 ± 10.2
NPI-C** anxiety	-4.0 ± 11.1	-7.5 ± 10.4

NPI-C** aggression	-2.6 ± 7.8	-0.5 ± 4.8
NPI-C** dysphoria	-6.3 ±10.7	-5.3 ± 13.0
NPI-C** elation / euphoria	-0.6 ± 1.0	0.1 ± 1.9
NPI-C** apathy /indifference	-5.4 ± 10.3	-10.4 ± 17.2
NPI-C** disinhibition	-0.9 ± 9.7	1.8 ± 8.3
NPI-C** irritability /liability	-1.9 ± 18.6	-3.8 ± 12.2
NPI-C** aberrant motor disturbance	-2.1 ± 5.7	1.8 ± 5.1
NPI-C** sleep disorders	-5.4 ± 5.3	-1.8 ± 5.8
NPI-C** appetite and eating disorders	-2.0 ± 2.2	-2.6 ± 6.0
NPI-C* aberrant motor vocalizations	2.4 ± 4.2	-1.3 ± 5.6

Neuropsychiatric Inventory-Clinician rating scale, NPI-C* Clinician Impression
Neuropsychiatric Inventory-Clinician rating scale, NPI-C** Caregiver distress

Week 6 change showing (-) means worsening for cognitive measures such as Standardised Mini-Mental State Examination, sMMSE; Addenbrooke's Cognitive Examination-III, ACE-III; Hopkins Verbal Learning Test, HVLT and clinical measures such as Dementia Quailty of Life measure, DEMQOL and DEMQOL-Proxy.

Week 6 change showing (-) means improvement for clinical measures such as Neuropsychiatric Inventory-Clinician Impression, NPI-C; Bristol Activities of Daily Living Scale, BADLS and Cohen Mansfield Agitation Inventory-short form, CMAI-SF.

REFERENCES:

Brandt, J. (1991). The hopkins verbal learning test: Development of a new memory test with six equivalent forms. *Clinical Neuropsychologist*, 5, 125-142.

Bucks, R. S., Ashworth, D. L., Wilcock, G. K. and Siegfried, K. (1996). Assessment of activities of daily living in dementia: development of the Bristol Activities of Daily Living Scale. *Age and ageing*, 25, 113-120.

Cohen-Mansfield, J. and Billig, N. (1986). Agitated behaviors in the elderly. I. A conceptual review. *J Am Geriatr Soc*, 34, 711-721.

Cummings, J. L. (1997). The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology*, 48, S10-16.

de Medeiros, K.*, et al.* (2010). The Neuropsychiatric Inventory-Clinician rating scale (NPI-C): reliability and validity of a revised assessment of neuropsychiatric symptoms in dementia. *Int Psychogeriatr*, 22, 984-994.

Lingjaerde, O., Ahlfors, U. G., Bech, P., Dencker, S. J. and Elgen, K. (1987). The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl*, 334, 1-100.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D. and Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34, 939-944.

Molloy, D. W. and Standish, T. I. (1997). A guide to the standardized Mini-Mental State Examination. *Int Psychogeriatr*, 9 Suppl 1, 87-94; discussion 143-150.

Olin, J. T.*, et al.* (1996). Clinical evaluation of global change in Alzheimer's disease: identifying consensus. *J Geriatr Psychiatry Neurol*, 9, 176-180.

Smith, S. C.*, et al.* (2007). Development of a new measure of health-related quality of life for people with dementia: DEMQOL. *Psychol Med*, 37, 737-746.