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Parkinson's Disease and Dementia with Lewy Bodies, Patients Under Treatment with Standardized Extracts Enriched in Cannabidiol and Cannabigerol: Descriptive Observations in Preparation for a Phase 2a Clinical Trial

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Abstract

Background: Cannabis-based formulations are now widely used by patients with neurological and psychiatric problems but no studies have been published on the clinical utility of CBD/CBG enriched extracts for parkinsonism's symptoms.

Objectives: To describe preliminary clinical data collection of PD and DLB patients under CBD/CBG medical prescription.

Methods: Review of electronic records of 14 PD and 5 DLB patients. Four extracts were available 1) CBD broad spectrum (100 mg/mL) 2) CBD/CBG broad spectrum (100 mg/mL 2:1) (3) CBD/CBG (2:1) + THC0.3% full spectrum (100mg/mL) 4) CBD+THC0.3% full spectrum (100 mg/mL). All the patients received authorization from ANVISA (Brazil) to import the formulations for medical use. Outcomes of each unmet need (UMN) were tabulated and graded.

Results: Demographics: PD N = 14 (10 male). DLB: N = 5 (3 male). Mean age: PD: 76.2 yrs. (46 - 94). DLB: 82.2 yrs. (83 - 92). Disease duration: PD (6.57 yrs.), DLB (4.2 yrs.); PD H/Y stage (3); PD levodopa dose: 490 mg (150 - 900). Mean daily doses: PD CBD: 65.17 mg (8.33 – 125 mg), CBG: 22,50 mg (4.16 - 50 mg), THC: 2,32 mg (0,75 - 4,5 mg). DLB CBD: 52 mg (5 - 100 mg). CBG: 8,75 mg (2,5 - 15 mg), THC: 0,225 mg. Positive results were seen for RBD, insomnia, anxiety, and pain. All pain responders were on CBG and/or THC formulations. Hallucinations were also attenuated in both patient groups. Safety and tolerability were favorable in this small sample.

Conclusions: Future clinical trials in Parkinson's disease and DLB with cannabinoids should focus on their potential benefit for associated anxiety, and pain. The potential anti-psychotic effects of CBD and CBD/CBG should also be further evaluated in a phase 2a clinical trial.

Keywords: *Cannabidiol; Cannabigerol; Parkinson's Disease; Dementia With Lewy Bodies; Medical Cannabis*

Abbreviations

ANVISA: National Agency of Health Vigilance (Brazil); ASTM: Accelerated Aging of Sterile Barrier Systems for Medical Devices; CBD: Cannabidiol; CBG: Cannabigerol; CPGF: Cannabidiol Pharmaceutical Grade Formulations; DBS: Deep Brain Stimulation; DLB: Dementia with Lewy Bodies;

GMP: Good Manufactured Practice; ICB: Impulsive, Compulsive Behaviors; MS-HPLC: Mass Spectroscopy – High-Performance Liquid Chromatography; MCT oil: Medium Chain Triglycerides Oil;

PD: Parkinson's Disease; PIDG: Postural Instability with Gait Disability; RBD: Rem Sleep Behavior Disorder; THC: Δ9-Tetrahydrocannabinol

Introduction

In a A Manual of Diseases of the Nervous System published in 1888 the English neurologist William Gowers described the therapeutic role of "Indian hemp" (*Cannabis* indica) sometimes combined with opium- as an effective treatment for tremor in Parkinson's disease [1].

By the end of the 19th century, about 100 scientific papers on the potential therapeutic role of *cannabis* had been published [2]. During the early 20th century, Merck Laboratories (Germany), Burroughs-Wellcome (England), Bristol-Meyers Squibb (USA), Parke-Davis (USA), and Eli Lilly (USA) had in their portfolios of medications, extracts or tinctures of *cannabis* [3]. In 1937, the marijuana tax act – contrary to the American Medical Association's recommendation- led to the marked decline of medical use of *cannabis* and in 1941, *cannabis* was banned from the American pharmacopeia, being re-classified as a "planta non grata" [3].

Medical and scientific interest in *cannabis* resumed in the early '60s, with the discovery and synthesis of the principal psychoactive constituent of *Cannabis* sativa L. Δ9-tetrahydrocannabinol (Δ9-THC) [4]. In addition to Δ9-THC, other phytocannabinoids are present in different concentrations in Cannabis plant species including cannabidiol (CBD), cannabigerol (CBG), Δ9- tetrahydrocannabivarin (Δ9-THCV), and Δ9-cannabidivarin (CBDV) [5].

Cloning CB1 [6] and CB2 receptors [7] in the early 1990s opened the door to current knowledge about the endocannabinoid system – or the endocannabinoidome as it is sometimes referred to - an intricate network of biochemically related receptors, enzymes, and mediators. The endocannabinoid system's signaling involves regulating cells, tissues, and organs; organism homeostasis after insults; brain development and release of neurotransmitters and cytokines related to synaptic plasticity [8].

So far medicinal research has concentrated on CBD, the second most abundant constituent of *cannabis*. In contradistinction to Δ9-THC, CBD is not intoxicating, but it is psychoactive. It has a low affinity for CB receptors, acting as a CB1 partial antagonist and CB2 receptor inverse agonist [9]. It activates the TRPV1 channel [10] and 5-HT1A receptors [11]. It also is a GPR55 receptor antagonist [12] and inhibits the enzymatic activity of fatty acid amide hydrolase (FAAH) and the endocannabinoid anandamide's reuptake [13].

CBG has recently been evaluated *in vitro* and *in vivo* models [14]. It is a precursor of the most abundant cannabinoids and expresses an affinity for cannabinoid receptors between CBD and Δ9-THC [14]. It has unique interactions, acting as an alpha-2 adrenoreceptor agonist, potent 5HT1A receptor antagonist, and has a strong affinity for Peroxisome Proliferator-Activated Receptors (PPARs) [14]. Preclinical data has suggested that it may have potential for the treatment of inflammatory diseases [15], chronic pain [16], neoplastic diseases [17], PD [18], and Huntington's disease [19].

A recently published general patient survey of CBG-predominant cannabis use reported improvement in anxiety, chronic pain, depression and insomnia. Most respondents reported greater efficacy of CBG-predominant cannabis over conventional pharmacotherapy, with very few adverse side-effects [20].

Cannabidiol Pharmaceutical Grade Formulations (CPGF) such as Nabiximols (Sativex) (CDB/THC 1:1) [21] and purified cannabidiol (Epidiolex) [22] have been medically approved for the management of pain/spasticity in multiple sclerosis and for refractory epilepsy in Dravet/Lennox Gastaut syndromes.

In 2019 the National Health Surveillance Agency (ANVISA) in Brazil created a protocol for the registration of CPGF [23]. Only formulations produced in laboratories with the certification of Good Manufacturing Practices (GMP) and submitted formulations to pharmaceutical stability tests [24] could be registered for sale in pharmacies under medical prescription and formulations that fulfilled these standards received a temporary five-year license with the proviso that clinical trials must be performed to confirm efficacy [23]. *Cannabis* formulations can also be imported legally to Brazil, provided that they have received sanitary approval in the country of origin [25].

Clinical studies have demonstrated the potential of CBD in improving quality of life [26], reducing psychotic symptoms [27], and attenuating REM sleep behavioral disorder [28]. The high density of CB1 cannabinoid receptors in the basal ganglia also led to its investigation as a possible therapy in Parkinson's disease [29]. The synthetic cannabinoid nabilone has been reported as being mildly efficacious in levodopa-induced dyskinesias in one small clinical trial [30] but most of the few available studies have shown a limited role for phytocannabinoids with regard to improvement of motor symptoms in PD [31].

Recent clinical and preclinical evidence has suggested that CBD may have antipsychotic properties [32]. In contrast to some of the available anti-psychotic drugs CBD also appears to have no cardiac toxicity and does not increase the QT interval [33].

This paper describes pilot descriptive data collected in preparation for a controlled phase 2a study and describes the response of a small number of patients with PD and DLB patients treated with four different CBD or CBD/CBG formulations.

These standardized enriched extracts were developed specifically to meet the phytopharmaceutical registration rules issued by ANVISA. The extracts are produced in Florida-USA under GMP compliance (CBCeuticals Laboratories/Health Meds Laboratories) and imported to Brazil for compassionate use and approved by ANVISA (regulation number 335/2020). All formulations displayed MS-HPLC certification of analysis for each batch and passed the stability test protocol ASTM-F1980.

Methods

The medical records of 14 PD and 5 DLB patients were reviewed between April 2020 and June 2021. All patients were followed up in a single medical facility (Multidisciplinary Clinic- Botafogo- Rio de Janeiro/Brazil).

A neurologist (FHRC), specialized in movement disorders, established a PD diagnosis based on the Queen Square Brain Bank Criteria [34] and DBL using the Movement Disorders Society's criteria [35]. At the baseline clinical interview the main complaints were divided into motor or non-motor categories. The most frequent unmet needs for PD were disruptive RBD (N = 10), anxiety (n = 5), insomnia (n = 9), muscle-skeletal pain (5), hallucinations/cognitive decline (n = 5), motor fluctuations (n = 4), impulsive compulsive behaviors (n = 2). For DLB: disorientation with getting lost (n = 4), disruptive RBD (3), sleep fragmentation (n = 5), night agitation (n = 3), severe/complex hallucinations (n = 4), and delirium (5).

The chosen formulation was based on the clinical judgment and symptom profile of each patient. Four GMP certified formulations (Health Meds Laboratories-Brazil) were available for prescription as enriched standardized extracts: 1) Cannabidiol (CBD) broad spectrum (100 mg/mL) 2) Cannabidiol/Cannabigerol (CBD/CBG) (2:1) broad spectrum (100mg/mL) (3) Cannabidiol/Cannabigerol (CBD/CBG) (2:1) +THC 0.3% full spectrum (100mg/mL) 4) Cannabidiol (CBD)+THC 0.3% full spectrum (100mg/mL). All CBD or CBD/CBG formulations were pharmaceutical grade, which means purity, certificate of analysis, and stability tests issued by independent laboratories.

The formulations were presented in opaque bottles containing 60 ml. The excipient was Organic Medium Chain Triglycerides (MCT) oil (USP - FDA GRAS). A graduated micropipette was available in each of the bottles, protected by a child-proof cap. Each drop of the solution had 2.5 mg CBD or 2.5 mg CBD / CBG (2:1); therefore, 40 drops (1ml) contained 100mg of CBD or 100mg of CBD/CBG (2:1). In THC 0.3% formulations each 1 mL delivered 3 mg of THC.

All patients were instructed to take the trial medication with food. The introduction of the first dose was always at night, respecting the concept of "start low and go slow" (2.5 mg - 12.5 mg CBD at bedtime) with a focus on determining the lowest dose for symptomatic control. The dose titration was variable, depending on the target symptoms.

A pharmacist oversaw pharmacovigilance by phone or by email contact.

Follow-up medical consultations took place every 2-3 months when target symptoms were reassessed, and a physician made dosage adjustments.

Ethical considerations

The study received ethics committee approval and institutional board review (CEP/UNESA: 45936121.2.0000.5284 / Plataforma Brasil). All patients received the prescriptions based on ANVISA resolution number 335 - which regulates the importing process of *cannabis* derivatives to Brazil (25). Patients signed an informed consent form and completed an electronic form made available on the regulator's official website. ANVISA issued an exceptional, compassionate import authorization for each patient - valid for two years- which contains the prescribing physician's name, the formulation, and the patient's name associated with a code generated by the regulatory agency. The laboratory staff could assist the patients or their guardians during the entire ANVISA clearance process. All personal data followed the guidelines of the Federal Government's data protection law.

Measurements and calculations

Data were extracted from the records of each patient (*ComAmigo*® version 9.16.61 www.cebim.com.br*)*. The variables age, gender, disease duration, follow-up duration, H/Y stage, levodopa, and cannabinoids doses were tabulated in the SPSS (version 18 for MAC) for calculating the means and standard deviations (SD). The concomitant use of psychotropic medications was noted in each case.

The specific and general outcomes in relation to the patient's major complaints and unmet needs were graded as GOOD, MODERATE, LIMITED, or INEFFECTIVE. Symptoms graded as GOOD/MODERATE were deemed satisfactory, and LIMITED/INEFFECTIVE were considered unsatisfactory. Changes in drug prescription regimes were noted, focusing on recording reduction or withdrawal of sedatives or neuroleptics.

Data was sent to a medical auditor (ELT) and another neurologist specializing in movement disorders (MS) to check and discuss any inconsistencies.

Results

The mean age of the PD patients was 72.6 years (42 - 94) and for DLB , 82.2 years. (8 3- 92). Most of the patients were male (PD = 10 and DLB = 3). The disease duration was 6.57 years. (± 2.70) for PD and 4.2 years. (± 1.30) for DLB. The follow-up duration was 3.78 months (± 5.63) for PD and 4.2 months (± 1.30) for DLB. The average levodopa dose was 490 mg (± 212), with a mean H / Y of 3 (± 0.84) in the PD group (Table 1 to 6).

	PD	DLB
Patients (n)	14	5
Age (years)	72.6 (42-94)	82.2 (83-92)
Gender n (%) (male)	10 (72)	3 (60)
Disease Duration (yrs) (SD)	6.57 (± 2.70)	4.2 (± 1.30)
Follow up duration (months) (SD)	3.78 (± 5.63)	4.2 (± 1.30)
Hoehn and Yahr (SD)	3 (± 0.84)	
Mean Levodopa dose mg (SD)	490 (± 212)	
Daily CBD mean dose mg (SD)	67.50 (± 38.6)	52 (± 44.8)
Daily CBG mean dose mg (SD)	22.50 (± 16.82)	8.75 (± 8.33)
Daily THC mean dose mg (SD)*	2.32 (± 1.46)	0.02 mg (± 0.01)
Daily THC mean dose mg (SD)**	0.83 (± 2.24)	0.02 mg (± 0.01)

Table 1: *Patients' characteristics.*

*(SD=Standard deviation). CBD= Cannabidiol CBG= Cannabigerol THC= Δ9-tetrahydrocannabinol. PD= Parkinson's disease. DLB= dementia with Lewy bodies. * n=5 PD and n=1 DLB patients on THC containing formulations. ** All patients included.*

#	Diagnosis	Gender		Age	Disease Duration (years)	Disease Stage H/Y	Comorbidities	Initial Concurrent Drugs	
#1	PD	M	63	6	6	2	Essential hypertension, Chronic pain (coxofemural osteoarthritis)	Levodopa 600mg/day; Rasagiline 1mg/day, domperidone 10mg t.i.d, Amantadine 100mg t.i.d, Rotigotine 8mg/day,	
#2	PD	M	69	5	1	3	Obesity	Levodopa 900mg/day, Rasagiline 1mg/day, entacapone 1 gr/dia, clonazepam 2mg, duloxetin 60mg, domperidone 10mg t.i.d	
#3	PD	F	88	7	5	3	Essential hypertension, osteoarthritis (low back pain)	Levodopa 400mg/day, sertraline 100mg//day, zolpidem 10mg bedtime	
#4	PD	M	46	6	5	2		Levodopa 600mg/day; Rasagiline 1mg/day, domperidone 10mg t.i.d, pramipexol 4.5 mg/day	
#5	PD	M	53	6	1	3		Levodopa 500mg/day; Rasagiline 1mg/day, domperidone 10mg t.i.d, clozapine 12.5mg/day	

#6	PD	M	80	12	6	4	PD Dementia (PIGD)	Levodopa 400mg/day, Rasagiline 1mg/day, Rivastigmine Patch 9,5mg/day, melatonin 5mg
#7	PD	M	94	8	3	4	Osteoarthritis	Levodopa 400mg/day, Rasagiline 1mg/day
#8	PD	M	77	6	4	2.5	Essential hypertension	Levodopa 300mg/day, Rivastigmine Patch 9,5mg/day
#9	PD	M	90	12	1	5	Advanced pharyngeal neoplasm (palliative care)	Levodopa 400mg/day, Rasagiline 1mg/day, Rivastigmine Patch 9,5mg/day, melatonin 5mg, escitalopram 5mg/day, clonazepam 0.25mg
#10	PD	M	85	6	2	3	Colostomy (past bowel diverticulum perforation)	Levodopa 900mg/day, amantadine 100mg/day, venlafaxine 75mg/day, Lithium (prescribed by another physician)
#11	PD	F	88	4	5	3		Levodopa 500mg/day; Rasagiline 1mg/day, amantadine 100mg/day, Lorazepan 2mg bedtime
#12	PD	F	79	2	5	2	Hypothyroidism= levothyroxine 125mcg/day	Levodopa 150mg/day, rasagiline 1mg/day, domperidone 30 mg/day, fludrocortisone 0.2 mg bedtime
#13	PD	M	80	5	5	3		Levodopa 300mg/dia, Rotigotine 4mg/day, galantamine 16mg/day, zolpidem 6.25mg, quetiapine 75mg bedtime,
#14	PD	F	75	7	4	3	Thrombophilia	Levodopa 500mg/day; Rasagiline 1mg/day, Rotigotine 8mg/day, amantadine 100mg/day, venalafaxine 75mg/day, domperidone 30mg/day, dabigatran

Table 2: *PD: demographics, comorbidities, and initial concurrent treatment. PIGD=Postural instability with gait disability. PD= Parkinson's disease.*

Number	Diagnosis	Formulation	Daily CBD Dose (mg)	Daily CBG Dose(mg)	Daily THC Dose(mg)
#1	PD	Cannabidiol + Cannabigerol 2:1 (100mg/mL) + THC 0.3%	100	50	4,5
#2	PD	Cannabidiol (100mg/mL)	100		
#3	PD	Cannabidiol + Cannabigerol 2:1 (100mg/mL)	41.66	20.83	
#4	PD	Cannabidiol (100mg/mL) + THC 0.3 %	25		0,75
#5	PD	Cannabidiol + Cannabigerol 2:1 (100mg/mL)	12.5		
#6	PD	Cannabidiol (100mg/mL)	50		
#7	PD	Cannabidiol + Cannabigerol 2:1 (100mg/mL)	8.33	4.16	
#8	PD	Cannabidiol (100mg/mL)	125	0	
#9	PD	Cannabidiol + Cannabigerol 2:1 (100mg/mL) + THC 0.3%	33.33	16.66	1,5
#10	PD	Cannabidiol (100mg/mL)	75	0	
#11	PD	Cannabidiol + Cannabigerol 2:1 (100mg/mL) + THC 0.3%	41.66	20.83	1,87
#12	PD	Cannabidiol (100mg/mL) + THC 0.3 %	100		3
#13	PD	Cannabidiol (100mg/mL)	100		
#14	PD	Cannabidiol (100mg/mL)	100		
#1	DLB	Cannabidiol (100mg/mL)	100		
#2	DLB	Cannabidiol (100mg/mL)	100		
#3	DLB	Cannabidiol + Cannabigerol 2:1 (100mg/mL)	30	15	
#4	DLB	Cannabidiol + Cannabigerol 2:1 (100mg/mL) + THC 0.3%	25	2.5	0.025
#5	DLB	Cannabidiol (100mg/mL)	5		

Table 3: *Formulations and daily doses of each patient.*

#	Diagnosis	Unmet Need Before Treatment	Effect On Unmet Needs	Overall Effect	Comments
#1	PD	1)Pain**** and compulsion 2) insomnia 3) RBD* 4) Anxiety***	GOOD	GOOD	Rigidity reduction only on 4.5 mg of THC
#2	PD	1)Motor fluctuations (freezing of gait) 2) Low back pain 3) RBD	INEFFECTIVE	LIMITED	The patient discontinued treatment after one month. Improvement in sleep duration.
#3	PD	1) insomnia 2) RDB* 3) pain 4) Mild hallucinations (benign)**	GOOD	GOOD	Zolpidem withdrawn. Fewer episodes of somnambulism.
#4	PD	1) Problematic wearing off phenomenon 2) impulsivity (compulsive internet stock market "day trade" behavior 3) severe anxiety 4) RBD*/insomnia	MODERATE	LIMITED	No impact on motor symptoms / no impact on wearing off/ Drowsiness in doses >50mg CBD/THC 0.3%. Patient on preparation for DBS.

#5	PD	1) Problematic motor and "non-motor wearing-off phenomenon. Severe tremor 2) Transient psychosis/hallucinations (induced by dopaminergic overstimulation: suicide attempt	LIMITED	LIMITED	Clozapine withdrawal. No effect on the extreme motor fluctuations. Patient on preparation for DBS.
#6	PD	1) Hallucinations** 2) cognitive decline 3) RDB*/ wandering 4) severe gait disability	GOOD	GOOD	Remains without the use of neuroleptics. No impact on motor symptoms. Add on effect on hallucinations
#7	PD	1) Insomnia 2) Nocturnal pain **** 3) non-motor nocturnal fluctuations (anxiety***) 4) RBD*	GOOD	GOOD	Market attenuation of non-motor nocturnal fluctuations
#8	PD	1) Anxiety*** 2) Complex hallucinations** 3) Insomnia 4) RBD*	GOOD	GOOD	Stable without neuroleptics. No impact on motor symptoms
#9	PD	1) Hallucinations** 2) Cognitive decline 3) Severe rigidity 4) Insomnia	GOOD	MODERATE	Palliative care in end of life. No effect on rigidity. Morphine sparing effect. No end-of-life delirium. Patient died comfortably
#10	PD	1)Gait balance problems 2) Apathy 3) Mild depressive symptoms	GOOD	GOOD	Better on the balance after lithium withdraw.
#11	PD	1) Severe pain****: Dopamine agonist-induced cervical dystonia 2) anxiety*** 3) RBInsomniania	GOOD	GOOD	Other actions for pain management: immediate pramipexol withdrawal and US-guided botulinum toxin cervical injection.
#12	PD	1) Severe levodopa/rasagiline induced nausea and hypotension 2) Anxiety	GOOD	GOOD	Nausea improvement. Orthostatic hypotension controlled with fludrocortisone
#13	PD	1) Moderate hallucinations**2) RBD* and insomnia 3) Cognitive decline (PDD)	GOOD	GOOD	Quetiapine dose unchanged. Add on effect on hallucinations.
#14	PD	1) wearing off (freezing of gait) 2) Cognitive decline 3) RBD*/ benign hallucinations** 5) Anxiety*** (despite venlafaxine use) 6) pain (knee arthrosis)	GOOD	MODERATE	No impact on wearing off phenomenon RDB symptom abolished/marked improvement of hallucinations

Table 4: *RBD= Rem sleep behavior disorder. *RBD symptoms abolished and substantial increment in sleep duration. ** Marked improvement in hallucinations. *** Marked response in anxiety symptoms. **** Pain responders. PD= Parkinson's disease.*

#	Diagnosis	Gender	Age	Disease Duration (yrs)	Disease Stage H/Y		Comorbidities	Initial Concurrent Drugs
#1	DLB	M	83	3	2	N/A	Coronary disease (past coronary angioplasty with stents implants)	Levodopa 400mg/day, melatonin 10mg bedtime, rivastigmine Patch 4,5 mg/day, eszopiclone 2mg bedtime
#2	DLB	F	71	3	5	N/A		Rivastigmine Patch 9,5 mg/day, melatonin 5mg day, memantine 10 mg bedtime, mirtazapine 15mg bedtime, alprazolam 0.5mg bedtime
#3	DLB	M	87	4	4	N/A	Venous insufficiency, deep vein thrombosis / paroxysmal atrial fibrillation, anticoagulant: dabigatran	Donepezil 10mg/day, memantine 20mg/day, escitalopram 10mg/day, alprazolam 2mg/day, levodopa 400mg/day
#4	DLB	F	78	6	5	N/A	Severe weight loss	Rivastigmine Patch 4,5 mg/day, trazodone 25mg/day, olanzapine 2,5mg, eszopiclone 2mg/day
#5	DLB	M	92	5	5	N/A	Arterial peripheral vascular disease, Pulmonary fibrosis, recurrent urinary tract infections with delirium (prolonged double J catheter)	Rivastigmine Patch 13.3 mg/day, clozapine 12.5mg bedtime, venlafaxine 75mg/day

Table 5: *DLB: demographics, comorbidities, and initial concurrent treatment. DLB= Dementia with Lewy bodies.*

#	Diagnosis	Unmet need before treatment	Effect on unmet needs	Overall Effect	comments
#1	DLB	1) Severe sensorium fluctuation 2) wandering, agitation, and RBD 3) Severe complex hallucinations, 4) Drug hypersensitivity.	INEFFECTIVE	INEFFECTIVE	No overall benefit
#2	DLB	1) Severe complex hallucinations*** 2) wandering** 3) anxiety	MODERATE	LIMITED	Limited effect on the speed of cognitive decline. The patient still deteriorating on multiple other aspects: Language visuospatial skills

#3	DLB	1) Severe hallucinations*** 2) wandering** 3) RBD* 4) fast cognitive decline and sundowning	GOOD	MODERATE	Mild mental confusion / somnolence in doses above 45mg of CBD/CBG 2:1. Stable on the actual dose.
#4	DLB	1) Severe hallucinations*** 2) wandering** 3) RBD*, fast cognitive decline and sundowning 4) severe parkinsonism 5) severe weight loss	GOOD	GOOD	Olanzapine and eszopiclone was withdrawn
#5	DLB	1) Insomnia and nocturnal agitation 2) Marked parkinsonism with gait balance problems 3) Cognitive fluctuations *** 4) pain (arterial insufficiency)	GOOD	MODERATE	Clozapine was withdrawn

Table 6: **RBD responders. ** Marked improvement in wandering. *** Marked response in hallucinations. DLB= Dementia with Lewy bodies.*

Regarding prescribed formulations, PD patients were on CBD enriched n = 6, CBD/CBG 2:1 enriched n = 3, CBD/CBG 2:1 enriched + THC 0.3% n = 3, CBD/THC 0.3% n = 2 full spectrum. DBL patients were on CBD enriched n = 3, CBD/CBG 2: 1 enriched n = 1, CBD/CBG 2: 1 enriched +THC 0.3% n = 1.

The average CBD dose was 67.5 mg for PD (± 38.6) and 52mg (± 44.8) for DLB. The CBG dose was 22.5 mg for PD (± 16.82) and 8.7mg (± 8.33) for DLB. The average THC dose was 2.32 mg for PD (± 1.46) and 0.02 mg for DLB (± 0.01); this variable was calculated only in patients using THC-containing formulations. Considering all patients in the PD and DLB groups, the average THC dose was 0.83 mg (± 2.24) for PD, and 0.025 mg (± 0.01) for DLB.

Marked improvements were observed on RBD (9/10), insomnia (9/9), anxiety (5/5) in the PD patients. There was also improvement in reported pain (3/5), impulsive-compulsive behaviors (ICB's) (2/2), and visual hallucinations (6/7). All pain responders were on formulations with CBG and THC.

RBD symptoms were markedly reduced in 9 patients (PD#1, PD#3, PD#4, PD#6, PD#7, PD#8, PD#11, PD#13, PD#14). For instance, PD # 14 had a long history of sleep disturbance having kicked her husband several times during vivid dreams episodes. All her symptoms vanished after 50mg CBD nocte. The dose was titrated to 50mg twice a day, and this patient also experienced a marked attenuation of late afternoon visual hallucinations.

A marked response was also observed in the five patients whose anxiety was considered an important factor in reducing quality of life (PD#1, PD#7, PD#8, PD#11, PD#14). PD#11 had experienced several months of pain and *antecollis* dystonic posture. The patient was in great distress, markedly anxious, and experiencing severe insomnia. Dopamine agonist-induced cervical dystonia was initially considered as a cause of pain and abnormal cervical posture. Pramipexole was suspended and rasagiline and low dose amantadine were slowly introduced but with no improvement. After four weeks, CBD/CBG 2:1 + THC 0.3% formulation was started and titrated to 62.5 mg (25 drops) at night. A marked improvement in anxiety symptoms and sleep disturbance was promptly observed.

A modest response in musculoskeletal pain was observed only in those patients with formulations that contained CBD or CBG with or without THC (PD#1, PD #7, and PD#11). CBD isolated formulations did not produce analgesic effects in PD#2 and PD#14.

An antipsychotic effect occurred in six patients (PD#3, PD#6, PD#8, PD#9, PD#13, PD#14)- usually associated with improved sleep quality and decreased anxiety symptoms.

In DLB patients, improvements in wandering (3/4), disruptive RBD (2/3), sleep fragmentation (4/5), night agitation (2/3), and hallucinations (4/5) were reported and in two patients (DLB#4 and DLB#5) with delirium and agitation it was possible to discontinue sedative and anti-psychotic medication. DLB#3 showed a marked reduction in visual hallucinations, despite having drowsiness with CBD/CBG 2:1 dose above 45 mg (18 drops at dinner). The caregiver also reported attenuation of cognitive fluctuations, marked improvement in sleep, and no visual hallucinations at the current dose.

Concerning DLB#1, intervention with CBD enriched (THC Free) was considered ineffective. The patient was looked after by his elderly wife and many different interventions had produced little benefit. After changing the care plan- which trained night caregivers- his cognitive fluctuations were much attenuated.

No improvement in motor symptoms was observed, except in patient #1 (CBD/CBG 2:1 + THC 0.3%) who reported reduced stiffness with 4.5mg THC daily. PD #5 had severe off tremor that failed to respond This patient is currently undergoing a evaluation for a DBS surgical implant.

Discussion

This study provides tentative support for earlier studies demonstrating phytocannabinoids' potential in managing some PD non-motor symptoms [31]. Anxiety, sleep disorders, and visual hallucinations responded beneficially to the four formulations.

The high average age in both groups, multiple comorbidities, concurrent use of multiple drugs, and relatively long disease duration in this study reflects the real-world patient population and encourages further controlled studies.

The response rate was high in sleep disorders, especially in the disruptive forms of RBD and PD/DLB sleep fragmentation. In PD, 9 of 10 patients had their RBD symptoms markedly reduced which is in line with some previous clinical reports [28]. Cholinergic deficits underline RBD and sleep disruption both in PD and DLB [36]. Preclinical studies have shown that CBD enhances *in vivo* acetylcholine levels from the basal forebrain and increments sleep duration [37].

Current RBD drug treatment options are melatonin and clonazepam [38] - the latter although highly effective can interfere with cognition and normal sleep architecture, and put patients at greater risk of falls [39].

The oldest PD patient (PD#7) was 94 years old and experienced a marked reduction of non-motor nocturnal fluctuations (pain, anxiety attacks) and improved sleep quality. Mild drowsiness occurred, however, in CBD/CBD (2:1) dose above 12.5 mg (5 drops)- indicating that dose titration should be individualized and symptom-focused.

To emphasize the significant variability of doses, PD#1, relatively younger, reached the total amount of 100 mg of CBD, 50 mg of CBG, and 4.5 mg of THC, with an excellent tolerability profile. There has been a report of improved sleep quality, decreased ICB traits (compul-

sive painting), and reduced muscle stiffness (need a reference here). Previous studies have also shown that doses of isolated CBD between 75 mg - 300 mg can improve PD patients' quality of life with an excellent safety profile [31].

Our study emphasizes the need for lower doses in all formulations, compared with previous reports in the elderly, and provides some support for cannabinoids exerting an *entourage* effect [40].

Another intriguing finding was the attenuation of hallucinations and psychotic symptoms. Hallucinations are known harbingers for dementia and increased mortality in PD patients [41]. Current treatment options are restricted to cholinomimetics and atypical antipsychotics such as clozapine In DBL, the use of neuroleptics is even more challenging due to neuroleptics hypersensitivity and neuroleptics have been associated with increased mortality in dementias [39].

A moderate response to pain was observed only in those on CBG or THC formulations (PD#1, PD#7, PD#11), supporting the view that combinations of cannabinoids may be best for this indication [40]. .

The safety profile and tolerability were excellent. The adverse effects reported were drowsiness during titration (PD#5 and PD#7), promptly reversed with dose reduction.

Even though the data were structured for each patient, no previously validated scale was applied in this study and there was no randomization. The outcomes were assessed exclusively based on the patients' or caregivers' reports in a semi-structured clinical interview conducted by a neurologist with training in movement disorders. On the other hand, checking the data by an independent neurologist and a medical auditor helped with data transparency.

Finally, the present work was possible due to Brazilian legislation changes. The recent ANVISA regulations provided access to standardized extracts via import process, although not yet available in the Brazilian National Health System under universal coverage [25]. ANVISA regulations paved the way for developing randomized clinical studies, which will soon establish these novel formulations' efficacy in various medical indications [23].

Perspectives for Future Studies

These encouraging findings in managing sleep disorders and mental health problems in elderly patients with Parkinson's disease encourage the need for well-conducted randomized clinical trials with CBD or CBD/CBG to examine its antipsychotic potential. Further trials with phytocannabinoids for tremor and l-dopa induced dyskinesias in PD should also be conducted.

Conclusions

This report describes the potential of CBD/CBG formulations for non-motor symptoms treatment in PD and DLB- such as anxiety, sleep disorders, visual hallucinations, impulsivity, and pain and will be helpful in designing a phase 2a randomized placebo-controlled clinical trial.

Conflict of Interests

Prof. Flávio Rezende works part-time in Research and Development (R&D) for Health Meds Laboratories (Brazil) and advisor physician for Cbeuticals Laboratories (USA).

Simone Pellegrino de Oliveira works full-time as a Pharmacist for Health Meds-Brazil.

Eduardo Rydz works full-time as Director of Access for Health Meds-Brazil.

Dr. Gabriel de Castro Micheli works part-time as an MSL (Medical Science Liaison) for Health Meds Laboratories.

Jaron Gladstone is CEO and Founder of CBCeuticals Laboratories- Coral Springs- Florida- United States.

Brian Ebner is V.P of production at CBCeuticals Laboratories – Coral Springs- Florida- United States.

Prof. Mariana Spitz has no conflict of interest to declare.

Dr. Elio Tanaka has no conflict of interest to declare.

Prof. Andrew Lees has no conflict of interest to declare.

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Volume 14 Issue 5 May 2022