Reduction of Apathy and the Associated Caregiver Distress using a Combination of Tetrahydrocannabinol and Melatonin in Participants with Dementia due to Alzheimer's Disease

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Takeaway message: IGC-AD1, a Tetrahydrocannabinol (THC) and melatonin combination, has the potential to treat Apathy in Alzheimer's disease.

Background:

Apathy is one of the most frequent and long-lasting neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD).[1] Studies reported a prevalence of apathy in AD ranging from 19% to 88%, with an overall mean prevalence of 49%, related to caregiver distress, decreased quality of life, and increased morbidity.[2] Apathy is defined as loss of or diminished motivation in at least two of three domains, including goal-directed behavior, cognitive activity, and emotion, sufficiently causing significant impairment in everyday life.[2]

There is no FDA-approved drug to treat apathy in AD. While some off-label medications and behavioral interventions are used to treat apathy, the effects are often limited and lack in-depth research to support these approaches.[3,4] Thus, apathy is emerging as a treatment target for pharmacological and non-pharmacological interventions.

Brain amyloid-β (Aβ) deposition, one of the hallmarks of AD, has been reported to be correlated with apathy.[5] Tetrahydrocannabinol (THC) and melatonin showed preclinical data supporting its effect to decrease Aβ40 levels in N2a/APPswe cells in a dose-dependent manner, through direct interaction with Aβ peptide and aggregation inhibition.[6,7] In addition, an in vivo study in aged APP/PS1 transgenic mice revealed that low-dose THC treatment significantly decreased the expression of Aβ oligomers.[8] Preclinical data suggest the potential effect of THC and melatonin on apathy management through an Aβ-associated mechanism.

Thus, this study investigated the effect of our investigational drug, IGC-AD1, a combination of THC and melatonin, on the reduction in NPI-Apathy scores and NPI Caregiver Distress (NPI-D) scores in Phase I clinical trial.

Methods:

Thirteen Participants diagnosed with mild (15.4%) to moderate (84.6%) AD (NIA-AA criteria and clinical history) participated in a three-cohort Phase 1 trial with MAD for safety and tolerability (10 Active, 2 Placebo per cohort, 81.5 ± 5.5yrs, 69.2% women). In Cohorts 1, 2, and 3, 1ml of IGC-AD1 was administered QD, BID, and TID, respectively, for 14-days (EOT) (**Fig. 1**). There was a 4-day minimum washout period between cohorts. Solicited and non-solicited adverse events (AEs) and the vital signs of all participants were monitored during each 14-day period.

In each cohort, seven Participants (5-Active, 2-Placebo) had apathy at baseline, as rated by the NPI-Apathy.

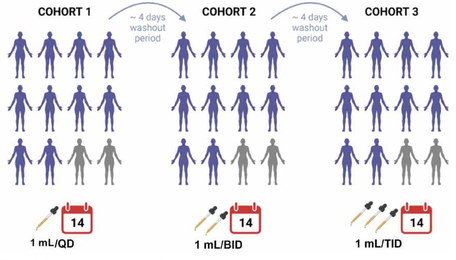

Figure 1. Phase I clinical trial design.
Purple: Active Participants, gray: Placebo Participants

Behavioral test: NPI-Apathy / NPI-Distress (NPI-D) were administered at baseline (Day 1) and EOT (Day 15).

Statistical analysis: The average score differences between Day 1 and Day 15 were calculated using either two-sided Wilcoxon signed-rank tests or paired t-tests, depending on the data distribution. The differences between placebo and active groups were assessed with Mann-Whitney U tests or independent t-tests (R-Studio, dplyr).

Results:

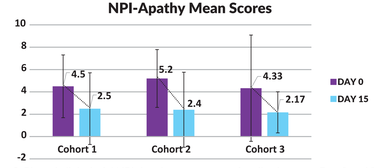

Figure 2. Phase I clinical trial NPI-Apathy mean scores for all cohorts on Day 0 and Day 15

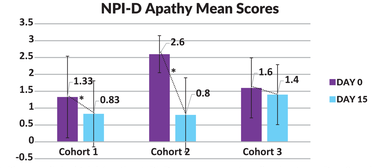

Figure 3. Phase I clinical trial Apathy, NPI-D mean scores for all cohorts on Day 0 and Day 15
*Statistically significant (p<0.05)

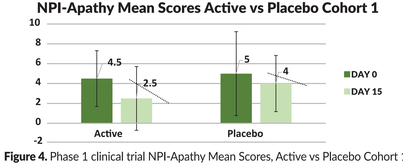

Figure 4. Phase 1 clinical trial NPI-Apathy Mean Scores, Active vs Placebo Cohort 1

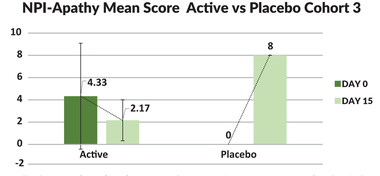

Figure 5. Phase 1 clinical trial NPI-Apathy Mean Scores, Active vs Placebo Cohort 3

Table 1. NPI-Apathy and NPI-D mean scores and statistical analysis between Day 0 and Day 15

Cohort	N	Intervention	NPI	DAY 0	DAY 15	D15-D0	% Reduction	P value	A vs P
1	6	Active	NPI-Apathy	4.5 ± 2.81	2.50 ± 3.21	-2 ± 2.53	44.4	t = -1.936 p = 0.111	t = 0.514 p = 0.625
	2	Placebo		5 ± 4.23	4 ± 2.83	-1 ± 1.41	20.0	t = -1 p = 0.5	
	6	Active	NPI-D	1.33 ± 1.21	0.83 ± 0.98	-0.50 ± 0.55	37.6	V = 26.5 **p = 0.028**	V = 0.300 p = 0.584
	2	Placebo		3 ± 0	2 ± 1.41	-1 ± 1.41	33.3	t = -1 p = 0.5	
2	5	Active	NPI-Apathy	5.2 ± 2.59	2.40 ± 3.36	-2.80 ± 3.27	53.8	V = 6 p = 0.102	-
	5	Active	NPI-D	2.60 ± 0.55	0.80 ± 1.1	-1.80 ± 0.84	69.2	V = 15 **p = 0.041**	-
3	6	Active	NPI-Apathy	4.33 ± 4.76	2.17 ± 1.84	-2.17 ± 3.87	49.9	t = -1.372 p = 0.228	t = 2.433 p = 0.059
	1	Placebo		0 ± 0	8 ± 0	8 ± 0	800	-	
	5	Active	NPI-D	1.60 ± 0.89	1.40 ± 0.89	-0.20 ± 1.1	12.5	V = 2 p = 0.655	t = 1.833 p = 0.141
	1	Placebo		0 ± 0	2 ± 0	2 ± 0	200	-	

In Cohort 1, the mean NPI-Apathy at baseline and EOT were 4.5 and 2.5, respectively (mean difference=-2, p=0.091). In Cohort 2, the mean NPI-Apathy at baseline and EOT were 5.2 and 2.4, respectively (mean difference=-2.8, p=0.087). In Cohort 3, the mean NPI-ap at baseline and EOT were 4.33 and 2.17, respectively (mean difference=-2.17, p=0.228).

Results for NPI-D: (Cohort-1: mean difference=-0.5, 37.6%, p=0.028; Cohort 2: mean difference=-1.8, 69.2%, p=0.041; Cohort 3: mean difference=-0.2, 12.5%, p =0.655). No serious AEs, no deaths, and no dropouts due to AEs were reported. No major changes in concomitant medications were observed.

Conclusion:

As IGC-AD1 contains THC, the results are intriguing. In previous studies, cannabis use has been associated with increased apathy.[9] In Cohort 1, Cohort 2, and Cohort 3, apathy as measured by NPI-Apathy reduced by 44.44%, 53.84%, and 49.88% respectively. These results were not statistically significant (p>0.05) but were clinically significant[10] (reduction in NPI-Apathy ≥30%).

A larger multi-site, placebo-controlled, double blind, randomized, Phase-2 study is currently underway wherein the NPI-12 will be used to measure among other neuropsychiatric symptoms, Apathy.

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