Reduction of Neuropsychiatric Symptoms and Associated Caregiver Distress Using a Tetrahydrocannabinol and Melatonin Combination in Dementia Due to Alzheimer's Disease

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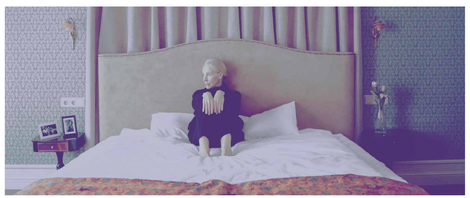
Takeaway message: IGC-AD1, and oral combination of tetrahydrocannabinol (THC) and melatonin, administered to participants with Alzheimer's Disease (AD) showed a significant reduction in neuropsychiatric symptoms and caregiver distress, as evaluated by the Neuropsychiatric Inventory - 12 (NPI-12).

Background:

Neuropsychiatric Symptoms (NPS) are features of Alzheimer's Disease (AD) that affect about 90% of AD patients and are a main cause of institutionalization. [1, 2] Figure 1 shows NPS measured by the NPI-12. [2] Even though NPS affect a large number of AD patients, existing medications for NPS often have black-box warnings and detrimental side effects. [3, 4] High doses of THC have shown mixed results in previous studies by either marginally improving NPS or having no impact. [5, 6] Furthermore, high doses of THC have caused unwanted side effects. In contrast, this study administered low doses of THC and melatonin (IGC-AD1), to evaluate their safety and effect on NPS and caregiver distress using the NPI-12. [7]



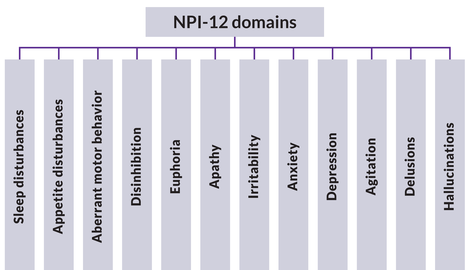


Figure 1. NPI-12 domains [7]

Methods:

Twelve patients diagnosed with mild (15.38%) to moderate (84.62%) 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, 81.5 ± 5.5yrs, 69.2% women). In Cohort 1, 2, and 3, one milliliter of IGC-AD1 was administered once a day (QD), twice a day (BID), and three times a day (TID), respectively, for 14 days, end of trial (EOT) (**Fig. 2**). 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.

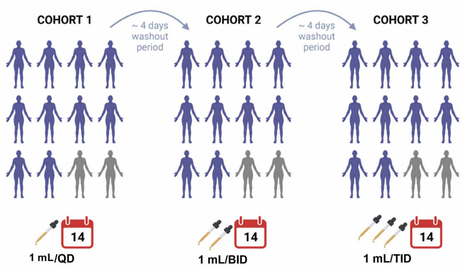


Figure 2. Phase 1 clinical trial implementation. Purple indicates the number of active participants nd gray the number of placebo participants.

Behavioral test: NPI-12 / NPI-Distress (NPI-D) were administered at Baseline (Day 1) and EOT (Day 14). [7]

Statistical analysis: A Shapiro-Wilk test was used to determine normality. Based on the normality of the data, either a T-test or a Wilcoxon signed-rank test was applied to compare the difference between scores on Baseline and EOT for each of the cohorts. In addition, the differences between placebo and active groups were assessed with Mann-Whitney U tests or Independent T-tests (R-Studio, dplyr).

Results:

Change between Baseline and EOT in the NPI-12 and NPI-D scores.
For each cohort, baseline scores were compared to determine whether the effect of IGC-AD1 persisted after each washout period. A Kruskal-Wallis test was used to determine the baseline differences for the cohorts in NPI-12 and NPI-D scores. There was no statistically significant difference between cohort baselines on the NPI-12 (H= 2.16, p = 0.34) or NPI-D (H = 4.03, p = 0.133) scores (**Fig. 3**). This suggests that there was no lingering effect from one cohort to another.

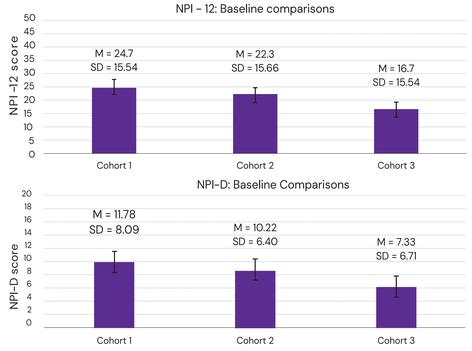


Figure 3. Average baseline scores comparisons between cohorts.
No significant differences for the NPI-12 and NPI-D. Means (M) and standard deviations (SD) are represented at the top of each bar. Error bars represented SEM.

There were statistically significant differences in the mean NPI-12 scores between Baseline and EOT in all the cohorts, per the Wilcoxon signed-rank test results (Cohort 1: mean difference = -16.7 ± 16.07, V = 55, p=0.005; Cohort 2: mean difference= -9.8 ± 10, V = 42, p = 0.024; Cohort 3: mean difference=-8.1 ± 8.08, V = 35, p = 0.021). Similarly, the distress scores were significantly decreased on EOT as compared to Baseline in all the cohorts (Cohort 1: mean difference = -7 ± 6.53, V = 44, p = 0.01; Cohort 2: mean difference = -6.40 ± 5.82, V = 45, p = 0.009; Cohort 2: mean difference = - 3.10 ± 3.81, V = 26.5, p = 0.034) (**Fig. 4**).

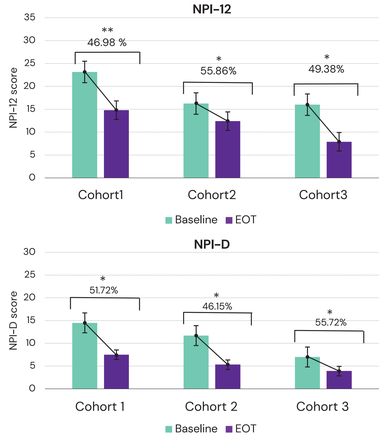
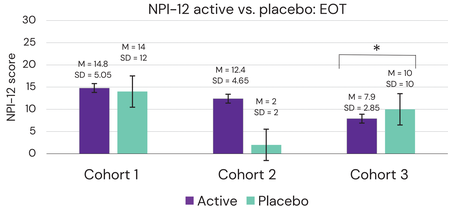


Figure 4. Average scores comparisons for Baseline and EOT in Cohort 1, Cohort 2, and Cohort 3 NPI-12 and NPI-D. Percentage reduction from baseline is presented above. Error bars represented SEM. Statistical significance markers: * p < 0.05, ** p < 0.01.

Active vs. placebo comparisons at EOT
Comparisons of NPI-12 scores between the placebo (N = 2) and the active groups (N = 10) showed significant difference for Cohort 3 (U=35, p = 0.017) but not for Cohort 1 or 2. Caregiver distress showed no statistically significant differences between groups for all three cohorts (**Fig. 5**).



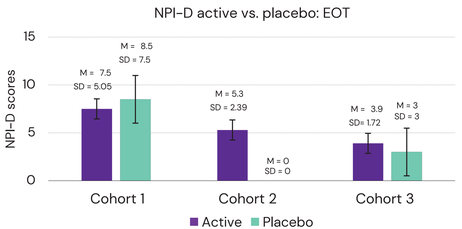


Figure 5. Active vs. placebo average scores comparisons EOT in NPI-12, NPI-D. Means (M) and standard deviations (SD) are represented at the top of each bar. Error bars represented as SEM. Statistical significance markers: * p < 0.05, ** p < 0.01.

Conclusion:

At all three dosages, IGC-AD1 led to a clinically and statistically significant reduction in NPS and caregiver distress as measured by the NPI-12. The active and placebo score comparison in this study suggests that IGC-AD1 may be efficacious at reducing NPS in AD patients. However, in future trials, a larger sample size and comparable active/control groups would provide more conclusive results. To address this, a randomized 146-patient, multi-site, double-blind, placebo-controlled, Phase 2 trial is currently underway to evaluate IGC-AD1's efficacy at reducing NPS such as agitation in AD.

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References:

1. Alzheimer's & dementia (New York, N. Y.), 2020, 6(1), e12016.
2. International journal of Alzheimer's disease, 2011, 721457.
3. Frontiers in neurology, 2022, 13, 877143.
4. Drugs in R&D, 2019, 19(2), 93–115.
5. Neurology, 2015, 84(23), 2338–2346.
6. Frontiers in Neuroendocrinology, 2022, 65, 100986.
7. J. Geriatric Psych and Neur, 2020, 33(2):73-84

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