Reduction of Agitation and 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, an oral solution combining Tetrahydrocannabinol (THC) and melatonin, showed safety, tolerability, and clinically significant reduction in NPI Agitation and Caregiver Distress (NPI-D) scores as measured by the NPI-12.

Introduction:

Agitation is a common neuropsychiatric symptom in Alzheimer's Disease (AD) patients.[1] It affects roughly 40% to 76% of AD patients.[2, 3] The International Psychogeriatric Association (IPA) defines it as recurrent emotional distress associated with excessive motor activity, verbal aggression, or physical aggression that is severe enough to impair personal relationships, social functioning, and/or daily activities. [4]

Agitation is a determining factor with a direct influence on patients' quality of life not only because of its direct effect on the patient, but also because it, along with aggression and disinhibition, significantly contributes to caregiver distress.[5, 6] As these behaviors persist, the caregiver burden intensifies, resulting in potential consequences such as depression, sleep disturbances, and various emotional and behavioral disorders. Consequently, the patient-caregiver relationship is compromised, which increases the risk of inadequate care and potential mistreatment of the patient. [6]

This condition is thought to arise from CB1 receptor dysfunction, neurotransmitter imbalance, and neuroinflammation.[7, 8, 9] Unfortunately, most current drugs used to manage agitation in dementia patients are prescribed off-label, come with black box warnings, and are associated with undesirable side effects. Fortunately, IGC Pharma is addressing this issue by developing IGC-AD1, an oral combination of THC and melatonin. As a CB1 receptor agonist, THC modulates neurotransmitter release and reduces neurotransmitter imbalance.[9] Similarly, melatonin modulates neurotransmitters such as acetylcholine and glutamate.[10] IGC-AD1 has the potential to provide modulatory and neuroprotective effects, reduce oxidative stress, and mitigate neuroinflammation.[11]

The preliminary data from the IGC-AD1 Phase 1 Trial on the reduction of NPI Agitation and Caregiver Distress scores as measured by the NPI-12 is presented here.

Methods:

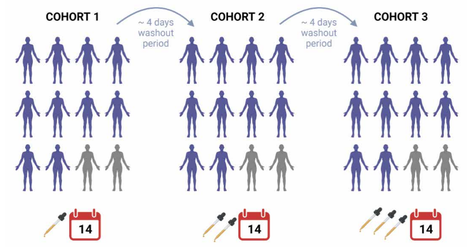
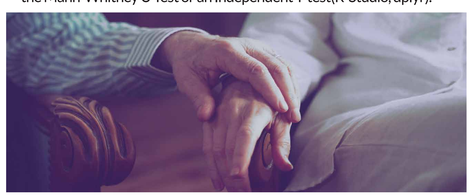


Figure 1. Phase 1 design. Purple are active participants and gray are placebo participants.

- 13 patients diagnosed with mild to moderate AD were included in this Phase 1, three-cohort, Multiple-Ascending-Dose (MAD) trial to evaluate the safety and tolerability of IGC-AD1 (IND146069, NCT04749563). Participants' mean age was 81.5 ± 5.5 years old; 9 women and 4 men.
- In Cohorts 1, 2, and 3, one milliliter of IGC-AD1 was administered QD, BID, and TID, respectively, for 14-days (EOT) with a 4-day minimum washout period between cohorts (Fig. 1). In all three cohorts, seven participants from the Active Group had agitation at baseline while only one participant from the Placebo Group had agitation in Cohort 1. NPI Agitation / NPI-D were administered at baseline (Day 1) and EOT (Day 15). Solicited Adverse Events, Unsolicited Adverse Events, and vital signs were monitored daily.
- The Shapiro-Wilk Test was used to determine normality. Based on the normality of the data, either a Paired T-test or the Wilcoxon Signed-Rank Test was applied to compare the difference between scores on Day 1 (Baseline) and Day 15 (EOT) for each of the cohorts. In addition, the differences between the Placebo and Active Groups were assessed with the Mann-Whitney U Test or an Independent T-test(R-Studio, dplyr).



Results:

Table 1. NPI Agitation and NPI-D Scores for All Cohorts on Day 0 and Day 15. Difference between Day 15 and Day 0, Percentage of Reduction, and Statistical Analysis of the Reduction.

Cohort	N	Intervention	NPI	DAY 0	DAY 15	D15-D0	% Red	P value	A vs P
1	7	Active	Agitation	4.71 ± 3.50	3 ± 3.22	-1.71 ± 1.8	**36.31**	V = 10 p = 0.063	t = 0.891 p = 0.407
	1	Placebo		3 ± 0	3 ± 0	0 ± 0	**0**	-	
	6	Active	NPI-D	3.67± 1.21	1.83± 1.47	-1.83± 1.17	**50.14**	V = 15 **p = 0.041**	t = 0.660 p = 0.538
	1	Placebo		3 ± 0	2 ± 0	-1 ± 0	**33.33**	-	
2	7	Active	Agitation	3.71± 2.36	1.29± 2.36	-2.43± 2.69	**65.23**	V = 10 p = 0.066	-
	7	Active	NPI-D	2.57± 1.27	0.86± 1.46	-1.71± 1.70	**66.54**	V = 10 p = 0.066	-
3	7	Active	Agitation	3 ± 2.45	1 ± 1.73	-2 ± 2.24	**66.67**	V = 10 p = 0.066	-
	7	Active	NPI-D	2.40 ± 0.89	1 ± 1.41	-1.40± 1.14	**58.33**	V = 10 p = 0.066	-

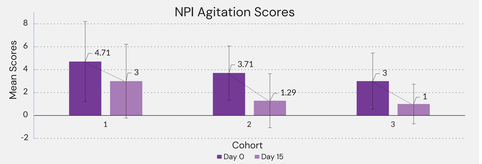


Figure 2. NPI Agitation Mean Scores: Day 0 and Day 15 for All Cohorts.

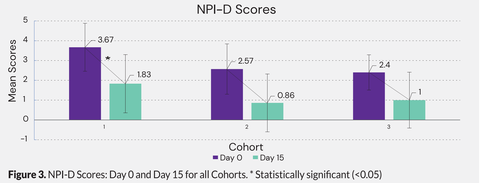


Figure 3. NPI-D Scores: Day 0 and Day 15 for all Cohorts. * Statistically significant (<0.05)

- Despite not being statistically significant, the P values for the difference in NPI Agitation scores between Day 0 and Day 15 for the 3 cohorts were between 0.063 and 0.066. The reduction in NPI-D scores in Cohort 1 showed statistical significance. However, in Cohort 2 and Cohort 3, the reductions were 66.54% and 58.33%, respectively, with P values of 0.063, which is likely due to the small sample size. Thus, future larger studies could potentially provide more statistically significant results.
- All cohorts demonstrated a clinically significant reduction (>30%) in NPI Agitation and NPI-D scores.

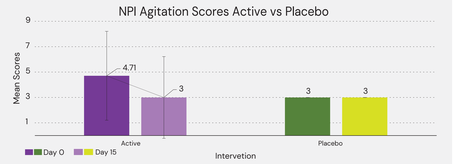


Figure 4. NPI Agitation Mean Scores: Day 0 and Day 15 for active vs placebo. Cohort 1.

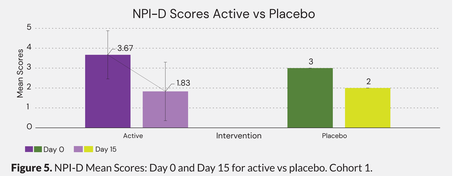


Figure 5. NPI-D Mean Scores: Day 0 and Day 15 for active vs placebo. Cohort 1.

- In the Active Group, the mean NPI Agitation and NPI-D scores decreased by 36% and 55%, respectively, while the Placebo Group's mean NPI Agitation and NPI-D scores decreased by 0% and 33%, respectively. This suggests that IGC-AD1 could be effective at reducing agitation and caregiver distress. However, a larger comparable control group could help produce more statistically significant results. No serious Adverse Events, deaths, or dropouts due to Adverse Events were reported. No major changes in concomitant medications were observed.

Conclusion:

IGC-AD1, a THC-melatonin combination, was safe, well-tolerated, and caused no serious Adverse Events. NPI Agitation and NPI-D scores indicate that IGC-AD1 may be efficacious at reducing agitation due to AD and associated caregiver distress. A study with a larger sample size and comparable active/control groups is needed. Currently, IGC Pharma is conducting a multi-center, randomized, double-blind, placebo-controlled, Phase 2 clinical trial to address those needs and investigate IGC-AD1's efficacy in treating agitation in AD patients.

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