Cannabis Treatment in Dementia Patients

A Phase II, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of Avidekel oil for the Treatment of Subjects with Agitation related to Dementia

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Conflict of Interest Statement

Lihi Bar-Lev Schleider is an employee of Tikun Olam, medical cannabis supplier in Israel

Not involved in data collection or analysis

We have nothing else to disclose

Background

Dementia:

- An acquired syndrome of decline in memory and other cognitive functions sufficient to affect daily life in an alert patient
- Progressive and disabling
- Not an inherent aspect of aging
- Different from normal cognitive lapses

Background

- Over **35 million** individuals currently have Alzheimer's Disease (AD) worldwide
- Prevalence : 6%–8% of people aged 65+ have AD
- Nearly 30% of those aged 85+ have AD

Background: Dementia and Neuropsychiatric Symptoms

- Neuropsychiatric symptoms, known to be **very common** among patients with AD
- Reported in more than 80 percent of subjects in most studies
- Agitation is one of the most common and challenging symptoms to treat
  - Occurring in 20-50% of patients with moderate to severe Dementia
- Associated with:
  - Caregiver burden
  - More rapid AD progression
  - Increased risk of falls
  - Weight loss
  - Mortality

Background: Management of Neuropsychiatric Symptoms

- **Atypical antipsychotic** agents are the preferred medications
  - For the management of psychosis or agitation
- Approximately **20% or more patients respond to active therapy**
- Patients with *inadequate responses* may benefit from therapy with
  - mood stabilizers
  - or antidepressants alone
  - or in combination with antipsychotic agents

Background: Cannabinoids

- Cannabinoids have the ability to
  - Protect neurons from the harmful impact of beta-amyloid
  - Reduce phosphorylation of tau protein
  - Enhance the expression of Neurotrophin
  - Regenerate nerve cells
  - Inhibit the activity of Acetylcholinesterase, which improves cholinergic transmission and hinders the development of the disease
  - Stimulate cannabinoid receptors on microglia cells which leads to a reduction in neural inflammation

The Endocannabinoid System Pathway

- CB1 receptors are highly abundant in the CNS
  - Particularly in cerebral cortex and hippocampus
    - Essential in learning and memory function
    - Affected by AD pathology

The Endocannabinoid System Pathway

- CB2 receptors are more abundant in the cells and tissues of the immune system
- Associated with decreases in the production of proinflammatory molecules
  - In vitro
  - And with the removal amyloid B plaques in the brain

The Endocannabinoid System

- Animal model studies
  - deletion of the CB1 gene is associated with cognitive impairment
- Several clinical studies
  - acute and chronic cannabinoids use are associated with cognitive impairment in
    - Healthy individuals
    - Patients population: multiple sclerosis and schizophrenia

Cannabis and Dementia

- Clinical data supports the beneficial of cannabinoids on behavioral symptoms in Dementia
- Volicer et al., demonstrated amelioration of behavioral symptoms in AD with Dronabinol-THC analogue
- Woodwart and co authors – significant reduction in agitation among Dementia patients with Dronabinol
- Broers and co authors- pilot study, reduction in agitation in THC/CBD oral medication

Cannabis and Dementia

In Ruthirakuhan meta-analysis on the natural and synthetic cannabinoids for agitation and aggression in AD:

- 7 articles and 1 abstract investigated synthetic cannabinoids or THC for the treatment of agitation and or aggression in patients with AD
- There were no clinical trials reporting on the efficacy of cannabidiol for agitation in patients with AD.
- 4 studies included patients with moderate AD
- 2 studies included patients with more severe stages of AD

Cannabis and Dementia

In Ruthirakuhan meta-analysis:

- There was no significant benefit of cannabinoids over placebo for the treatment of agitation
- There were no significant differences in change in neuropsychiatric symptoms between treatment groups
- Post hoc analysis: patients with greater AD severity demonstrated greater improvement in agitation when treated with cannabinoids

The Clinical Trial

The Efficacy and Safety of Avidekel oil for the Treatment of Subjects with Agitation related to Dementia

The Hypothesis

- Cannabis consumption will reduce behavioral disorders and restlessness in elderly patients with dementia

The Investigational Product

- The cannabis oil was made out of extract from the Avidekel strain and olive oil
- Avidekel oil containing Δ^9-THC and CBD in a 1:20 ratio at a concentration of 30% CBD and 1.5% Δ^9-THC
- Each Avidekel contains about 12 mg CBD and 0.6 mg Δ^9-THC
- The flowers that were used in making the oils were from one batch of the Avidekel strain

The Investigational Product

- A titration period of 6 weeks

- The initial dose was of 1 drop of oil under the tongue three times a day
- The maximal dose 21 drops three times a day, 12.6 mg of Δ^9-THC and 252 mg of CBD

- If an adverse reaction occurred, the patients were tapered down

Study Endpoints

Primary Efficacy Endpoint:

- The proportion of subjects achieving a CMAI ≥ 4-point decrease at week 16 compared to bassline
- **Cohen Mansfield Agitation Inventory CMAI-** caregiver rated questionnaire

  examines 29 agitated behaviors , on a 7 point scale

Cohen-Mansfield, J.. Agitated behavior in persons with dementia: the relationship between type of behavior, it's frequency, and it's distruptiveness. J Psychiatr Res. 2008 Nov ; 43(1) 64-69. doi:10.1016/j.jpsychires.2008.02.003

Study Endpoints

Secondary Efficacy Endpoints:

- Assessment of the proportion of subjects achieving a CMAI ≥ 4-point decrease during the treatment period at each time point
- Time to 4 point reduction in CMAI in treatment vs. control
- Mean change in CMAI score
- Mean change in NPI-NH- Neuropsychiatric Inventory- Nursing Home version
- Assessment of BPSD response to the treatment- Behavioral and Psychological symptoms of Dementia

Safety Endpoints

- Incidence and severity of adverse events (AE) and serious adverse events (SAE)

The Study Design

Duration of Treatment:

- The duration of study participation for each subject was expected to be 4 months:
  - a) up to 6 weeks (42 days) of dose titration;
  - b) another 10 weeks of relatively stable dose administration and assessment.

Inclusion Criteria

- Male or female subjects > 60 years old
- Diagnosis of Dementia (NCD) according to the DSM-V Criteria for at least 6 months prior to screening
- MMSE < 23
- Clinically relevant BPSD
  - operationally defined as Neuropsychiatric Inventory (NPI-NH) -agitation/aggression sub score of ≥3 at screening
- Documented history of clinically relevant BPSD
- Ability to participate in study evaluation and ingest oral medications

Exclusion Criteria

- The agitation/aggression is attributable to concomitant medications, environmental conditions or psychiatric condition
- Patients with severe heart disease
- Subjects suffering from Epilepsy
- Subjects suffering from anxiety disorder
- Subjects who had psychotic condition in the past OR suffering from psychosis, Schizophrenia OR family history of Schizophrenia OR any other mental disorder
- Patients suffering from alcohol and/or substance abuse

Enrollment Results

- 64 pts were eligible for enrollment
- 42 assigned to the active treatment
- 22 assigned to placebo

- 4 pts withdrew before treatment - 2 from the active treatment and 2 from placebo

- 8 pts withdrew :
  - 3 d/t difficulty in arriving
  - 2 died from unrelated causes
  - 1 d/t patient's family difficulty
  - 2 d/t other medical problems

Enrollment Characteristics

	Treatment (N=32)	Placebo (N=20)	P
Gender M F	 43.8% 56.2%	 25.0% 75.0%	.17
Age (range)	77.9 ± 8.8 (61-95)	80.6 ± 9.5 (64-92)	.30
Number of Medications	6.8 ± 2.8 (0-11)	6.6 ± 3.1 (2-12)	.83

Primary Outcome

CMAI reduction of ≥ 4 points at week 16:

Treatment Group	**71.9%**
Placebo Group	**30%**

- χ^2 **=8.75, P<0.003**

Secondary Outcome Baseline CMAI score

	Mean	SD
Treatment Group	57.28	17.34
Placebo Group	58.50	22.27

- No statistically significant difference in baseline CMAI between the two groups ($t(50)=0.83,\ p>.83$)

Secondary Outcome
Mean change in CMAI score

	Mean	Median	SD
Treatment Group	**-13.3**	**-8.0**	15.63
Placebo Group	**-2.3**	**-1.5**	9.13

- There was **a statistically significant difference** in the change between the 2 groups (t(50)=-3.20, **p<.002**).

Mean Change in Neuropsychiatric Inventory (NPI-NH) agitation/aggression sub score

	Baseline Level	Avg. Decrease
Treatment Group	6.0	**3.3**
Placebo Group	6.09	**1.1**

- There was **no statistically significant difference in baseline agitation level** (p>.95)
- **There was a statistically significant difference in mean change in agitation Neuropsychiatric Inventory (NPI-NH) agitation/aggression sub score** (**p <.02**)

Reduction in the number of medications

#Medications	Treatment Group	Placebo Group
Less	56.25%	52.6%
Same	31.25%	26.3%
More	12.50%	21.1%

- **There was no statistically significant difference in the change** (less/same/more) in the number of medicines at week 16 between the 2 treatment groups **(p=.71**)

Adverse Events (AE) , Serious Adverse Events (SAE)

- 2 pts died in the treatment group, d/t unrelated causes

Other Adverse Events:

- Mild Hyponatremia
- Increase in appetite
- Pruritus
- Hypotension

Summary

- Neuropsychiatric symptoms, known to be **very common** among patients with Alzheimer's disease
  - have been reported in more than 80 percent of subjects in most studies
- Agitation is one of the most common and challenging symptom to treat
  - Occurring in 20-50% of patients with moderate to severe Dementia

Our clinical trial shows that CBD rich cannabis oil can reduce agitation and the behavioral symptoms in dementia

The treatment is safe and efficient

Thank you for listening!!!