Designing a Randomized Placebo Controlled Cross-over Trial Investigating Nabilone as a Treatment for Agitation in Patients with Moderate-to-Severe Alzheimer's Disease

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Introduction & Background

- Agitation is a commonly occurring neuropsychiatric symptom (**NPS**) of Alzheimer's disease (**AD**)
- In patients with moderate-to-severe AD, agitation occurs in 20-50% of individuals
- Agitation is an important NPS to treat as it is associated with increased caregiver burden, AD progression, lack of physical health and weight loss
- Atypical antipsychotics are the current pharmacological recommendation for the treatment of agitation in AD. However, these medications have a poor side effect profile
  - Severe adverse events
  - Cardiovascular events
  - Mortality
  - Parkinsonism
- There is a need for a safer and more effective treatment

Proposed Study

We aim to investigate the safety and efficacy of nabilone for the treatment of agitation in patients with moderate-to-severe AD.

Study Population:

- Our goal is to recruit 40 participants with moderate-severe AD
- 20 patients from Sunnybrook Veterans' Long Term Care facility, 20 patients from outpatient psychiatry clinics

Table 1: Eligibility Criteria.

Inclusion	Exclusion
- Males or females ≥ 55yo - Moderate-to-severe AD (sMMSE ≤ 24) - Clinically significant agitation (NPI agitation subscale ≥ 3) - If treated with cognitive enhancing medications, dosage must be stable for at least 3 months	- Change in psychotropic medications less than 1 month prior to randomization - Contraindications to nabilone - Current significant cardiovascular disease - Presence of other psychiatric/neurological conditions

Trial Design

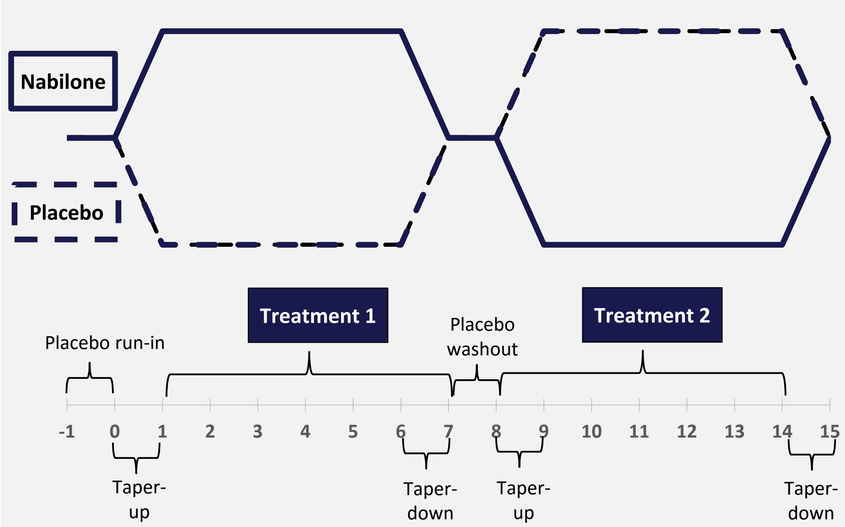

Figure 1: Trial Design.

Primary Outcome
- Agitation (CMAI)

Secondary Outcomes
- Behaviour (NPI), Cognition (sMMSE, SIB, ADAS-cog), Global Change (CGI-C)

Exploratory Outcomes
- Pain (PAIN-AD)
- Nutritional Status (MNA-SF)
- Safety (ADRs)
- Biomarkers (oxidative/nitrosative stress, inflammation, cholesterol metabolism)

CMAI: Cohen Mansfield Agitation Inventory, NPI: Neuropsychiatric Inventory, sMMSE: standardized Mini-Mental State Examination, SIB: Severe Impairment Battery, ADAS-cog: Alzheimer's disease Assessment Scale – cognitive scale, CGI-C: Clinician's Global Impression of Change, PAIN-AD: Pain Assessment in Advanced Alzheimer's disease, MNA-SF: Mini-Nutritional Assessment- Short Form, ADRs: Adverse Drug Reaction

Preliminary Results

Table 2: Baseline Demographics.

	Mean (±SD) (N=14)
Inpatients (%)	78.6
Male (%)	71.4
Age	88.2 (±8.3)
sMMSE	7.8 (±6.1)
SIB (N=13)	48.6 (±26.5)
ADAS-cog (N=1)	26
CMAI Baseline	69.8 (±21.1)
NPI – total severity	30.3 (±15.4)
PAIN-AD	2.8 (±1.8)
MNA-SF	1.2 (±0.6)

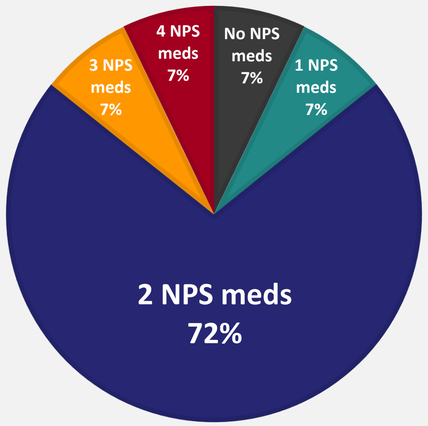

Figure 2: Distribution of patients on no, one or multiple psychotropic (NPS) medications. NPS medications include: antidepressants, antipsychotics, benzodiazepines, and hypnotic agents.

Table 3: Unblinded Outcomes.

	Mean (±SD) (N=14)
Number of ADRs	1.6 (±1.9)
Sedation (%)	57.1
Study discontinuations due to ADRs (%)	21.4
Clinical improvement (CGI-C) (%)	38.5
Improvement in CMAI scores (%)	62

Table 4: Medication History.

	Mean (±SD) (N=14)
Number of concomitant medications	13.8 (±4.9)
Number of psychotropic medications	2.2 (± 0.7)
Participants on antidepressants (%)	78.6
Participants on antipsychotics (%)	50
Participants on benzodiazepines (%)	7.1
Participants on hypnotic agents (%)	14.3

Conclusions

Preliminary data support that we are targeting an appropriate patient group given the participants' age, clinical characteristics, concurrent medication use, and severity of NPS. Improvements in agitation and global change suggest that nabilone may be an effective treatment for agitation in AD. However ADRs, specifically sedation should be monitored.

Acknowledgements

Supported by an operating grant from the Alzheimer's Society of Canada and the Alzheimer's Disease Discovery Fund. M. Ruthirakuhan is supported by a CIHR Doctoral Research Award.

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