Investigating placebo-effects in a randomized controlled trial in patients with moderate-to-severe Alzheimer's disease and agitation

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Introduction & Background

- Agitation is a commonly occurring neuropsychiatric symptom (**NPS**) of Alzheimer's disease (**AD**)
- 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
- A recent clinical trial with nabilone, a synthetic cannabinoid, has demonstrated efficacy for agitation in patients with AD
- Trial design considerations are essential to ensuring inclusion of patients with clinically significant and treatment-resistant agitation

Main Methodological Aim:

To describe the importance and impact of including placebo run-ins using the nabilone trial as an example

Study Design

Study Population:

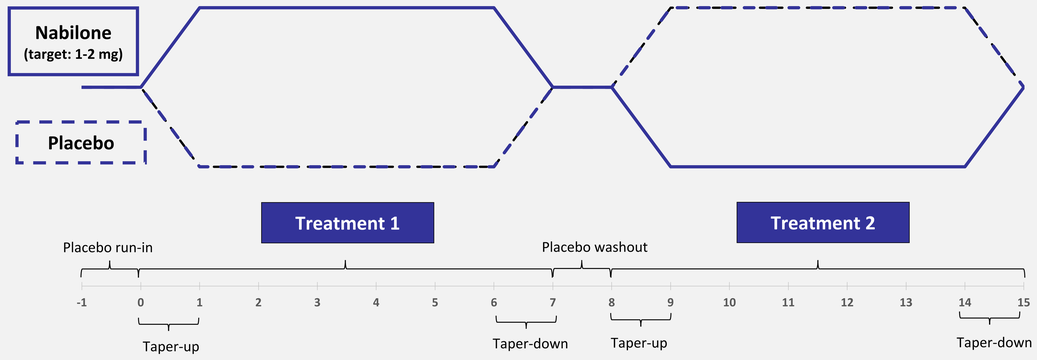
Table 1. Eligibility Criteria

Inclusion	Exclusion
- Males or females ≥ 55yo - Moderate-to-severe AD (sMMSE ≤ 24) - Clinically significant agitation (NPI agitation subscale ≥ 3) - Stable dose of cognitive enhancing medications for >3 months	- Change in psychotropic medications < 1 month prior to randomization - Contraindications to nabilone - Current significant cardiovascular disease - Presence of other psychiatric/neurological conditions

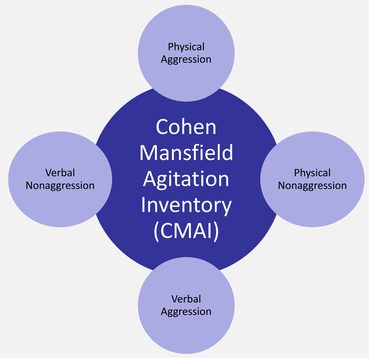
Analysis:

- Pairwise t-tests between screening and phase 1 baseline, and between the baselines of both phases were completed to investigate placebo and cross-over effects, respectively.

Trial Design



PRIMARY OUTCOME MEASURE:



Results

Table 2. Baseline demographics and cognitive scores (week 0)

	N=39
Inpatients (%)	71.8
Male (%)	76.9
Age (Mean ±SD)	87.3 ± 10.2
sMMSE (Mean ±SD)	6.5 ± 6.8
SIB (N=27) (Mean ±SD)	37.7 ± 30
ADAS-cog (N=3)	22.7± 3.1
PAIN-AD (Mean ±SD)	2.7 ±1.4
MNA-SF (Mean ±SD)	8.5 ±2.4

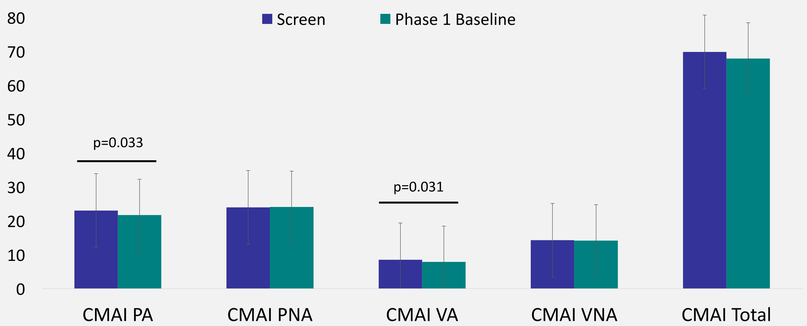
Table 3. Baseline behavioural scores (week 0)

	N=39
CMAI Baseline (Mean ±SD)	67.9 ± 18
NPI – total severity (Mean ±SD)	34.3 ± 16
NPI- agitation subscore (Mean ±SD)	7.2 ±3.2
% of patients who met IPA criteria for agitation	97.5

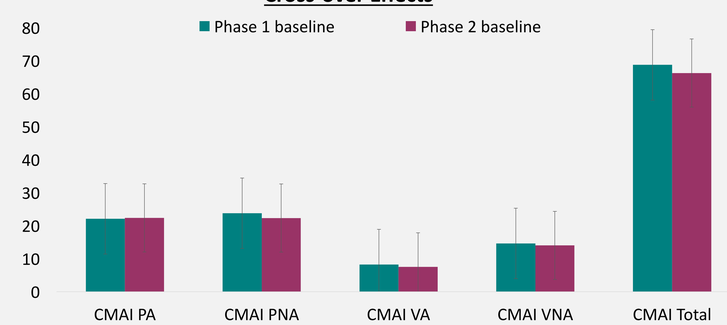
Table 4. Study characteristics.

	N=39
% of patients who reached *phase 1* max dose	72
% of patients who reached *phase 2* max dose	73

Placebo effects



Cross-over Effects



PA = physical aggression, PNA = physical non-aggression, VA = verbal aggression, VNA = verbal non aggression

There were significant PA and VA placebo-effects

There were no significant carry-over effects

Conclusions

Though there were no cross-over effects, the inclusion of a placebo run-in identified potential placebo-effects prior to baseline. Inclusion of a placebo run-in is advantageous in drug-based clinical trials as it identifies which patients are more likely to comply with treatment, and avoid unnecessary randomization of participants who respond to nonpharmacological interventions.

Acknowledgements

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