

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

Myuri Ruthirakuhan<sup>1,2</sup>, Nathan Herrmann<sup>1,3</sup>, Damien Gallagher<sup>3</sup>, Nicolas Paul L.G. Verhoeff<sup>4</sup>, Sandra E. Black<sup>1</sup>, Krista L. Lanctôt<sup>1,2,3</sup>

1) Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, ON, Canada

2) Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada

3) Department of Psychiatry, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

4) Department of Psychiatry, Baycrest Health Sciences Centre, Toronto, ON, Canada

### **Methodological Question Being Addressed:**

What is the importance of including a placebo run-in in a trial with nabilone in Alzheimer's disease patients with agitation?

### **Introduction:**

Pharmacological interventions for the management of agitation in Alzheimer's disease (AD) have modest benefits and high risk-profiles, spurring the search for new medications. Nonpharmacological interventions are at the cornerstone for interventions of agitation, however research has identified a lack of rigour and efficacy. We conducted a randomized placebo-controlled cross-over trial investigating the efficacy of the synthetic cannabinoid, nabilone for the treatment of agitation in AD. As agitation can be acute, improved with nonpharmacological interventions, and influenced by environmental factors, trial design considerations ensuring the inclusion of patients with persistent, clinically significant and treatment-resistant agitation is essential. To overcome this, single-blind placebo run-ins preceded each treatment phase. We aim describe the importance and impact of including placebo run-ins, using the nabilone trial design as an example.

### **Methods:**

This cross-over trial compared 6 weeks of nabilone (1-2 mg) to placebo, with 1-week single-blind placebo run-ins, preceding each phase. This trial selected for patients who had clinically significant agitation (Neuropsychiatric Inventory agitation $\geq$ 3) to ensure that patients were appropriately targeted for study intervention. The primary outcome was agitation, as measured by the Cohen-Mansfield Agitation Inventory (CMAI), and was administered at screening and baseline (BL). The CMAI measures 4 domains of agitation (physical aggression (PA), physical nonaggression (PNA), verbal aggression (VA) and verbal nonaggression (VNA)). Pairwise t-tests between the screening and BL of phase 1, and between the BL visits of both phases were completed to investigate the role of placebo effects, on CMAI total and CMAI subscores. While nonpharmacologic interventions are in place prior to enrollment, nonpharmacological interventions continue after the screening visit as caregivers are administered the CMAI and receive consultation from a study psychiatrist on potential nonpharmacological methods to alleviate agitation.

### **Results:**

Thirty-eight patients (mean $\pm$ SD age=87 $\pm$ 10, standardized Mini Mental Status Exam=6.5 $\pm$ 6.8, CMAI=67.9 $\pm$ 17.6, Neuropsychiatric Inventory total score=34.3 $\pm$ 15.8, 77% male) were randomized. Compared to screening, there was a significant decrease in CMAI PA (t(37)=2.21, p=0.03), and CMAI VA (t(37)=2.25, p=0.03) at BL. There were no significant differences in CMAI total, PNA, or VNA. There were no significant differences on CMAI total and subscores between the BL of each phase (all, p>0.05). All

patients had clinically significant agitation at screening and BL visits.

**Conclusions:**

These findings suggest that there may be placebo-effects as indicated by reduced PA and VA during the first placebo-run-in phase of our trial. The inclusion of a second placebo run-in ensured that the two BL visits were comparable to one another. Additionally, all patients had clinically significant agitation before and after the placebo run-in, confirming that patients were appropriately targeted for study intervention. Though only study staff are aware that the patient is not receiving active drug during the single-blind placebo run-in, the inclusion of a placebo run in allows us to identify which patients are more likely to comply with treatment, and avoid unnecessary randomization of patients who respond to nonpharmacological interventions.