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**CONTACT:** Alzheimer's Association AAIC Press Office, 312-949-8710, [aaicmedia@alz.org](mailto:aaicmedia@alz.org)  
Niles Frantz, Alzheimer's Association, 312-335-5777, [niles.frantz@alz.org](mailto:niles.frantz@alz.org)

## **FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2018**

### **NEW RESEARCH FOCUSES ON TREATING NON-COGNITIVE SYMPTOMS OF PEOPLE WITH DEMENTIA**

**Chicago, July 24, 2018** – New research presented at the Alzheimer's Association International Conference (AAIC) 2018 in Chicago focuses on the recent successes and ongoing challenges of drug and non-drug treatments for the non-cognitive symptoms experienced by people living with Alzheimer's dementia.

While the memory and thinking symptoms associated with the disease are the most well known, it is the behavioral and psychological symptoms of dementia (BPSD) — agitation, anxiety, apathy, depression, wandering, hallucinations, insomnia, incontinence, disinhibition — that often cause the greatest caregiving challenges and are the leading causes for placement in assisted living or nursing homes. Left untreated, these symptoms can accelerate decline and reduce quality of life.

At this time, the U.S. Food and Drug Administration (FDA) has not approved any drug treatments for these symptoms in people with Alzheimer's dementia. All drug treatments currently used are approved for other indications and prescribed for people with Alzheimer's "off-label."

"These underrecognized and undertreated symptoms in people with Alzheimer's and other dementias are often very difficult to live with and challenging to treat," said Maria Carrillo, PhD, Alzheimer's Association Chief Science Officer. "One of the 'untold stories' of Alzheimer's is the regular occurrence and overwhelming impact of these symptoms on the lives of people with Alzheimer's, their family members and caregivers."

"It is very important that as we continue to make advances in treating and preventing the memory and thinking symptoms of Alzheimer's and other dementias, we also focus on therapeutic strategies for the behavioral and other non-cognitive symptoms," Carrillo added.

The Alzheimer's Association recommends non-pharmacologic approaches such as psycho-social interventions as first-line alternatives to pharmacologic therapy for the treatment of dementia-related behaviors. These therapies include validation therapy, reminiscence and other personalized psychosocial interventions.

For example:

- Validate that the person seems to be upset over something.
- Separate the person from what seems to be upsetting.
- Engage in regular physical activity to potentially reduce irritability and aggressive behavior.
- Assess for the presence of pain, constipation or another physical problem.

Psychotropic medications (antipsychotics, antidepressants, anticonvulsants and others) may need to be considered when the dementia-related behavior has not responded to non-pharmacologic approaches, especially if it is causing physical or emotional harm to the person with dementia or caregiver(s), however they must be used with extreme care, and must be regularly evaluated to determine the appropriate time of cessation. The FDA found that using antipsychotics to treat dementia-related behaviors in elderly persons with dementia was associated with increased mortality.

### **Synthetic Cannabinoid Treatment Shows Improvement in Agitation in People with Alzheimer's**

Results of a randomized, double-blind clinical trial suggest that nabilone — a synthetic cannabinoid — may be effective in treating agitation in people with Alzheimer's disease. "Agitation, including verbal or physical outbursts, general emotional distress, restlessness, pacing, is one of the most common behavioral changes associated with Alzheimer's as it progresses, and can be a significant cause of caregiver stress," said Krista L. Lanctôt, PhD, Senior Scientist at Sunnybrook Health Sciences Centre and Professor of Psychiatry and Pharmacology/Toxicology at the University of Toronto.

Lanctôt and colleagues investigated the potential benefits of nabilone for adults with moderate to severe Alzheimer's dementia with clinically significant agitation. Over the 14-week trial duration, 39 participants (77 percent male, average age 87) received nabilone in capsule form (mean therapeutic dose=1.6 +/- .5 mg) for six weeks, followed by six weeks of placebo, with one week between each treatment period. In addition to measuring agitation, the researchers assessed overall behavioral symptoms, memory, physical changes and safety. They found that:

- Agitation improved significantly in those taking nabilone, compared to placebo, as measured by the Cohen-Mansfield Agitation Inventory (p=0.003).
- Nabilone also significantly improved overall behavioral symptoms, compared to placebo, as measured by the Neuropsychiatric Inventory (p=0.004).

The researchers also observed small benefits in cognition and nutrition during the study. More people in the study experienced sedation on nabilone (45 percent) compared to placebo (16 percent).

"Currently prescribed treatments for agitation in Alzheimer's do not work in everybody, and when they do work the effect is small and they increase risk of harmful side effects, including increased risk of death. As a result, there is an urgent need for safer medication options," said Lanctôt. "These findings suggest that nabilone may be an effective treatment for agitation; however, the risk of sedation must be carefully monitored. A larger clinical trial would allow us to confirm our findings regarding how effective and safe nabilone is in the treatment of agitation for Alzheimer's."

Note: Marijuana is not approved by the FDA for the treatment or management of Alzheimer's disease or other dementias. As medical marijuana use becomes more common, it is important to point out that much about its use in people with Alzheimer's or other dementias is unknown.

Marijuana is, essentially, an untested drug in Alzheimer's. There is currently no robust, consistent clinical trial data supporting the use of marijuana for treatment of Alzheimer's disease dementia — nor for related issues. The Alzheimer's Association believes that more research in this area is needed.

### **Lighting May Improve Sleep, Mood and Behavior in People with Alzheimer's**

Many people living with Alzheimer's disease and other dementias experience changes in their sleep patterns, insomnia, and daytime sleepiness. Mariana G. Figueiro, PhD, Director of the Lighting Research Center at Rensselaer Polytechnic Institute in Troy, NY, and colleagues tested whether a tailored lighting system could help to improve sleep, mood and behavior in people with Alzheimer's disease in nursing homes.

“Given that light/dark patterns are a person's primary cues to the current time, the constant dim light typically experienced by people living in residential care facilities may be an underlying cause of the sleep pattern disturbances so commonly found in this population,” said Figueiro.

To test this hypothesis, over a four-week period, lighting interventions were placed in areas where nursing home residents spent the majority of their waking hours and were left on from wake-up time until 6 p.m. Forty-three (43) residents (31 female, 12 male) participated in the short-term study, and 37 residents (25 female, 12 male) have completed the long-term study so far, all recruited from 10 nursing homes in the New York Capital District, Bennington, VT, and South Bend, IN.

Study participants experienced alternating periods of lighting that provided either high- or low-circadian stimulus for four weeks (short-term study) and six months (long-term study, successive four-week periods spaced by a four-week washout). The circadian stimulus (CS) metric, developed by the Lighting Research Center, characterizes a light source's effectiveness for stimulating the circadian system as measured by its capacity for acutely suppressing the body's production of the hormone melatonin (a well-established marker of the circadian system) after a one-hour exposure.

Both arms of the study used either a custom-designed LED light table or individual room lighting to deliver the intervention, depending on where the participants spent the majority of their time. Personal light meters were used to measure the light exposures received at the participants' eyes. Sleep disturbance, mood and agitation were also assessed using standardized questionnaires.

With the lighting intervention, researchers found that study participants who experienced the high-circadian stimulus showed significant decrease in sleep disturbance, depression and agitation. Positive effects observed in the short-term study continued to improve over the long-term study.

### **Beyond Anti-Psychotics: Exploring Efficacy and Harms of Z-Drugs for Sleep Disturbance**

Many people with dementia have problems sleeping. This affects their quality of life and that of the people who care for them. Non-benzodiazepine hypnotic “Z-drugs,” such as zolpidem, zopiclone and zaleplon, are often prescribed to help treat insomnia in older adults, but it is thought that they may cause problems such as falls, fractures, and increase confusion. People living with dementia are especially vulnerable and it is not clear whether Z-drugs are particularly harmful for them.

Chris Fox, MD, Professor of Psychiatry at Norwich Medical School University of East Anglia in Norwich, U.K., and colleagues analyzed existing data from the UK Clinical Practice Research Datalink, and from three clinical studies of people with dementia. They compared data for up to two years for 2,952 people with dementia who were newly prescribed Z-drugs with data for 1,651 who were not, in order to evaluate the benefits and harms of these medicines.

They found that the use of Z-drugs is associated with a 40 percent increased risk of any type of fracture, with risk increasing for those on higher doses. Z-drug use was also associated with a greater risk specifically of hip fracture. The study did not identify a higher risk of other effects, such as falls, infections or stroke.

“Fractures in people with dementia can have a devastating impact, including loss of mobility, increased dependency and worsening dementia,” said Fox. “We desperately need better alternatives to the drugs currently being prescribed for sleep problems and other non-cognitive symptoms of dementia. Wherever possible, suitable non-pharmacological alternatives should be considered, and where Z-drugs are prescribed, patients should receive care that reduces or prevents the occurrence of falls.”

### **The Alzheimer’s Association International Conference® (AAIC®)**

The Alzheimer’s Association International Conference (AAIC) is the world’s largest gathering of researchers from around the world focused on Alzheimer’s and other dementias. As a part of the Alzheimer’s Association’s research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

AAIC 2018 home page: [alz.org/aaic](http://alz.org/aaic)

AAIC 2018 newsroom: [alz.org/aaic/press](http://alz.org/aaic/press)

### **About the Alzheimer’s Association®**

The Alzheimer’s Association is the leading voluntary health organization in Alzheimer’s care, support and research. Our mission is to eliminate Alzheimer’s disease through the advancement of research, to provide and enhance care and support for all affected, and to reduce the risk of dementia through the promotion of brain health. Our vision is a world without Alzheimer’s. Visit [alz.org](http://alz.org) or call 800.272.3900.

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- Krista Lanctôt, PhD, et al. Nabilone Improves Agitation in Patients with Moderate-to-Severe Alzheimer’s Disease: Preliminary Results of a Placebo-Controlled, Double-Blind, Cross-over Trial. Funders: Alzheimer’s Drug Discovery Foundation; Alzheimer Society of Canada Research Program (Grant 15-17).
- Mariana Figueiro, PhD, et al. Tailored Lighting Intervention to Improve Sleep, Mood and Behavior in Alzheimer’s Disease Patients. Funder: U.S. National Institute on Aging.
- Chris Fox, MD, et al. Beyond Anti-Psychotics: Exploring Efficacy and Harms of Z-Drugs for Sleep Disturbance on the Progression of Key Dementia Outcomes. Funder: UK National Institute of Health Research.

Proposal ID: 22565

F4-02-04: New Approaches to the Treatment of Agitation Associated with Neurocognitive Disorders  
Weds., July 25, 8-9:30 am

### **Nabilone Significantly Improves Agitation/Aggression in Patients with Moderate-to-Severe AD: Preliminary Results of a Placebo-Controlled, Double-Blind, Cross-over Trial**

**Background:** Agitation is a common and persistent symptom in those with Alzheimer's disease (AD) and current pharmacotherapies have modest efficacy and/or poor safety. We assessed the efficacy and safety of nabilone for the treatment of agitation in AD.

**Methods:** This 14-week, randomized, double-blind, placebo-controlled cross-over trial compared 6 weeks of nabilone (1-2mg) to 6 weeks of placebo, with a 1-week washout between treatment phases. Moderate-to-severe AD patients (standardized Mini-Mental Status Exam (sMMSE)  $\leq 24$ ) with clinically significant agitation (Neuropsychiatric Inventory (NPI)-agitation/aggression subscore  $\geq 3$ ), were recruited from Long Term Care or outpatient psychiatry clinics. The primary outcome was agitation, as measured by the Cohen-Mansfield Agitation Inventory (CMAI). Secondary outcomes included safety, overall neuropsychiatric symptoms (NPI total), cognition (sMMSE) and global impression (Clinician's Global Impression of Change (CGIC)). Exploratory outcomes included pain (Pain Assessment in Advanced Dementia Scale (PAINAD)) and nutritional status (Mini-Nutritional Assessment-Short Form (MNA-SF)).

**Results:** Thirty-nine patients (mean  $\pm$  SD age =  $87 \pm 10$ , sMMSE =  $6.5 \pm 6.8$ , CMAI =  $67.9 \pm 17.6$ , NPI total score =  $34.3 \pm 15.8$ , 77% male) were randomized. The mean therapeutic dose of nabilone achieved was  $1.6 \pm 0.5$  mg. The estimated treatment difference in CMAI score was  $b = -4.0$  (95% CI -6.5 to -1.5,  $p = 0.003$ ) favouring nabilone with no cross-over ( $t(32) = 1.6$ ,  $p = 0.11$ ) or treatment-order ( $t(31) = 0.2$ ,  $p = 0.85$ ) effects. There were also significant differences in NPI-agitation/aggression ( $b = -1.5$ , 95% CI -2.3 to -0.6,  $p = 0.001$ ), NPI total ( $b = -4.6$ , 95% CI -7.5 to -1.6,  $p = 0.004$ ), and sMMSE ( $b = 1.1$ , 95% CI 0.1 to 2.0,  $p = 0.026$ ) favouring nabilone. On the CGIC, 47% and 23% of patients experienced improvement during the nabilone and placebo phases, respectively (McNemar's test,  $p = 0.09$ ). More patients experienced sedation on nabilone (45%) compared to placebo (16%) (McNemar's test,  $p = 0.02$ ), with no difference in treatment-limiting sedation (McNemar's test,  $p = 0.22$ ). There were treatment differences on the MNA-SF ( $b = 0.2$ , 95% CI 0.02 to 0.4,  $p = 0.03$ ), which favoured nabilone, but not on PAINAD ( $b = 0.03$ , 95% CI -0.22 to 0.27,  $p = 0.82$ ).

**Conclusions:** Nabilone significantly improved agitation, NPS, cognition and nutrition in patients with moderate-to-severe AD. However, the occurrence of sedation should be closely monitored. A larger trial with nabilone to provide confirmatory evidence regarding the efficacy and safety of nabilone in this patient group is warranted.

Krista Lanctôt, PhD

Email: [krista.lanctot@sunnybrook.ca](mailto:krista.lanctot@sunnybrook.ca)

Sunnybrook Research Institute, Toronto ON M4G 1R7, Canada

Proposal ID: O3-05-02  
Clinical: Non-pharmacological Therapeutic Interventions  
Tuesday, July 24, 8-9:30 AM

## **Tailored Lighting Intervention to Improve Sleep, Mood and Behavior in Alzheimer's Disease Patients**

**Background:** Light exposure during the day helps consolidate sleep and improve behavior in persons with Alzheimer's disease and related dementia (ADRD), but the light levels required are generally high and lighting fixtures that are currently available cannot deliver the level and spectrum of lighting that maximally affects the circadian system. The present study tested whether a tailored lighting intervention could improve sleep and behavior in ADRD patients living in long-term care facilities.

**Methods:** In the context of a crossover, repeated-measures design, we exposed subjects diagnosed with ADRD (Mini mental scale below 24) to an active (circadian stimulus, CS=0.3) and inactive (CS=0.1) tailored lighting intervention for successive 4-week periods, spaced by a 4-week washout period. The lighting intervention was added to spaces in which patients spent most of their waking hours and was energized from wake time until 6:00 pm. Calibrated personal light meters monitored exposures. Measures of sleep disturbances (Pittsburgh Sleep Quality Index, PSQI), mood (Cornell Scale for Depression in Dementia, CSDD) and agitation (Cohen-Mansfield Agitation Index, CMAI) were collected at baseline and during the last week of the intervention. The impact of long-term exposures (6 months) to the active light on these measures was also investigated.

**Results:** Compared to baseline and to the inactive lighting condition, the lighting intervention significantly decreased sleep disturbances, depression and agitation. The mean  $\pm$  SEM PSQI scores was  $10.4 \pm 0.4$  and  $6.4 \pm 0.5$  at baseline and after active intervention and  $9.7 \pm 0.5$  and  $8.0 \pm 0.4$  at baseline and after the inactive intervention. The mean  $\pm$  SEM CSDD scores was  $10.9 \pm 1.1$  and  $7.3 \pm 0.7$  at baseline and after active intervention and  $10.6 \pm 0.9$  and  $9.1 \pm 0.9$  at baseline and after the inactive intervention. The mean  $\pm$  SEM CMAI scores was  $43.6 \pm 2.5$  and  $37.5 \pm 1.9$  at baseline and after active intervention and  $41.5 \pm 1.8$  and  $40.4 \pm 1.9$  at baseline and after the inactive intervention. Sleep disturbance, depression and agitation scores continuously drop over the course of the 6-month lighting intervention.

**Conclusions:** When carefully delivered to patients' eyes and monitored with a calibrated instrument, daytime light can improve sleep, mood and behavior in nursing home residents with AD/ADRD.

Mariana Figueiro, PhD  
Email: [figuem@rpi.edu](mailto:figuem@rpi.edu)  
Rensselaer Polytechnic Institute, Troy NY 12180

Proposal ID: P3-023

## **Beyond Anti-Psychotics: Exploring Efficacy and Harms of Z-Drugs for Sleep Disturbance on the Progression of Key Dementia Outcomes**

**Background:** Approximately 60% of people with dementia (PwD) experience sleep disturbance including insomnia and excessive daytime sleeping. Hypnotic Z-drugs (zolpidem, zopiclone and zaleplon) are used to treat insomnia in the elderly but can cause adverse events e.g. falls and daytime cognitive impairment which might be particularly harmful for PwD. However, the safety and efficacy of Z-drugs in this group have not been fully evaluated. Given the importance of Z-drugs in offering respite from sleep disturbance for PwD and carers, and the type of adverse events, it is essential we understand the benefits and harms of these medications.

**Methods:** The ZED study (Z-drug Evaluation in Dementia; HTA 14/221/02, reporting June 2018) used existing data to estimate the impact of Z-drugs on adverse events, cognitive function, functional ability and quality of life in PwD. We utilised: (i) the UK Clinical Practice Research Datalink (CPRD; data routinely recorded by GPs), and (ii) data from three clinical studies of PwD. Stakeholders, clinicians, care workers and people affected by dementia prioritised outcomes including: falls and fractures, infections, stroke, neuropsychiatric symptoms, healthcare contacts and mortality (determined using CPRD), changes in cognition and function, changes in sleep disturbance and patient quality of life (determined using clinical studies data).

**Results:** The CPRD analysis includes 6,922 PwD with sleep disturbance and 3,102 prescribed Z-drugs followed for up to 2-years. The clinical study analyses include 3,057 PwD with 374 using Z-drugs followed for up to 11 years. We will present findings on the effects of Z-drug use on rates of the specified outcomes compared to the effects of other treatments (particularly antipsychotics and benzodiazepines) or no treatment.

**Conclusions:** Findings will provide guidance for sleep management in dementia. Prescribers will better understand the potential harms associated with medications for PwD. Furthermore, patients and carers of people with dementia will be better able to assess the benefits and harms of specific treatments, and have greater understanding of the likely consequences of using Z-drugs. This work could lead to improved care outcomes and quality of life, reduced hospital admissions, mortality, and institutionalisation for people who have dementia with sleep disturbance and their carers.

Chris Fox, MD

Email: [chris.fox@uea.ac.uk](mailto:chris.fox@uea.ac.uk)

University of East Anglia, Norwich NR4 7TJ , United Kingdom

Ian Maidment, PhD

Email: [i.maidment@aston.ac.uk](mailto:i.maidment@aston.ac.uk)

Aston University, Birmingham, United Kingdom