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Caffeine: a cup of care? An exploration of the relation between caffeine consumption and behavioral symptoms in persons with dementia

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SUMMARY

The word “dementia” derives from the Latin stem ‘demens’ and literally means ‘without mind.’ The medical term dementia covers over 100 diseases in which cognitive function deteriorates to a greater extent than seen in normal aging. Attention, planning, learning, memory, language, visual perception, spatial skills, social skills or other cognitive functions can all be affected. Patients with dementia can also display non-cognitive symptoms, e.g. aggression, agitation, anxiety, apathy, which are together referred to as behavioral symptoms. The etiology of behavior in patients with dementia is complex. Almost all patients with dementia will show behavioral symptoms at some point during the disease which decrease quality of life of the patient with dementia and place a high burden on informal caregivers. A higher caregiver burden often worsens the relationship between the caregiver and the patient with dementia, which in turn may increase the frequency and severity of behavioral symptoms. Quick and adequate management of behavioral symptoms in patients with dementia is necessary to prevent further harm for the patient, caregiver overload, avoidable nursing home admissions and avertible society costs.

To manage behavioral symptoms, the first step recommended in guidelines is the detailed analysis of the patients’ behavior, including contributory physical, psychological, social and environmental factors, after which interventions can be formulated. Although there is some evidence pharmacological agents can decrease behavioral symptoms in patients with dementia, the clinical effect is small and there is a high risk of severe adverse effects and even death. Psychosocial approaches have also been widely studied. Approaches like behavioral management techniques or cognitive stimulation are proven reduce behavioral symptoms. But in the management of behavioral symptoms, no standardized solution is currently available. All interventions that target behavioral symptoms must be tailored to the individual. However, even in the individualized approach nutritional factors are not regularly included as a possible cause or intervention.

Caffeine has been used for several centuries to influence behavior and the effects of caffeine on behavior in adults have been widely researched. It is now widely accepted that moderate caffeine consumption in healthy adults increases alertness, attention and cognitive function. It also elevates mood and reduces fatigue. A high caffeine consumption increases anxiety, can induce psychotic or manic symptoms and impairs sleep. As these effects differ between individuals, people normally adjust their consumption of caffeine based on their personal experience of (non-)beneficial (side) effects. Although the effect of caffeine on behavior in adults is widely accepted, the effect of caffeine on behavior in patients with dementia has not been properly investigated. As coffee is regularly consumed, widely available and most nursing homes do not have specific limitations or adjustments in the caffeine consumption of the residents, more insight in the relation between caffeine and behavior in patients with dementia is wanted.

Based on the known stimulatory effects of caffeine in healthy adults, it seems logical to assume that caffeine increases behavioral symptoms caused by general restlessness, anger and anxiety and increases sleeping difficulties during the night by suppressing fatigue in patients with dementia. The sleeping difficulties can lead to greater daytime sleepiness and a reversion of circadian

rhythm in patients with dementia which in its turn can also increase behavioral symptoms (e.g. irritability).

However, the opposite can also be hypothesized: caffeine consumption may favorably impact behavioral symptoms by improving concentration and lessening overstimulation due to an increase in alertness. Another possible favorable mechanism is the social aspect of caffeine consumption as social activities in general can reduce behavioral symptoms.

Both hypotheses were considered equally strong, therefore **the aim of this thesis** was to investigate whether there is a relationship between caffeine consumption and behavioral symptoms in patients with dementia, and (if a relationship exists) to determine the direction of any effects.

This thesis consists of four studies conducted in a stepwise design. First, two different studies were done to explore the hypotheses. If these studies showed signs of validation of the hypotheses, the second step would include more thorough research: a systematic literature review and a large multicenter cohort study. **Chapter 1** describes the observational pilot study which was performed to explore the possibility of a relationship between caffeine and behavioral symptoms in a group of elderly patients with dementia, with a focus on sleep, aggression, depression, anxiety, apathy, irritability and aberrant motor behavior. Over four days, these behavioral symptoms were measured using the Neuropsychiatric Inventory – Nursing Home edition (NPI-NH) and a sleep questionnaire, together with careful observation of caffeine consumption. In this sample of 29 elderly persons with dementia living in a special care unit a negative correlation between caffeine consumption and apathy and aberrant motor behavior (AMB) was found and positively correlated with getting out of bed at night. No significant correlations were found between caffeine and aggression, depression, irritability or anxiety. This exploratory study showed an association between caffeine consumption and some behavioral symptoms in a group of persons with moderately severe dementia.

Chapter 2 describes the second exploratory study. Because caffeine shows strong individual variation in effects on behavior in healthy adults, the second study was designed to examine the individual effects. In two persons with dementia, a high caffeine use and severe behavioral symptoms, caffeine consumption was regulated over a four-week period in a blinded crossover trial. The participants were served caffeinated or decaffeinated coffee in a predetermined order (C-D-D-C). Behavioral symptoms were then scored using the NPI-NH and the Cohan Mansfield Agitation Inventory (CMAI), with outcomes individualized per patient. Participant A was an 85-year-old woman with Alzheimer's disease and participant B was a 91-year-old women with mixed type dementia. Participant A had a decrease in her specific behavioral symptoms in the decaf weeks and a small increase on reintroduction of caffeine. In participant B no relation between caffeine and behavioral symptoms was found. This second study confirmed the association between caffeine and behavioral symptoms, but also showed the individual variation in effects.

The results of the two exploratory studies necessitated further research. **Chapter 3** describes the thorough and systematic literature review which was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines. The study proto-

col is registered at PROSPERO. The research question was formulated as “Does caffeine or coffee consumption influence neuropsychiatric symptoms, e.g. agitation, aggression, apathy, irritability, in elderly patients with dementia?”. Six (medical) journal databases (Medline (PubMed), Embase, Emcare, Cochrane, PsychInfo and Web of Science) and gray literature (GLIN, Greylit, AACN Research & Data center, WHO, OpenGray, HSO and Clinicaltrials.gov) were searched and more than 4000 articles were screened for relevance by two reviewers. After screening for eligibility, only seven articles remained. The seven studies differed in almost all facets: study type (from a case report to a RCT), publication date (ranging from 1976 tot 2018), methodology (qualitative and quantitative), the way of administering caffeine (beverages to injections) and measuring behavior. Most of the studies had methodological issues and despite a thorough analysis, no consistent conclusions could be drawn regarding caffeine consumption and behavioral symptoms. However, in each trial, the behavior of some participants seemed to be influenced by caffeine consumption both in a positive and in a negative way.

As fourth and final study, a large multicenter cohort study was conducted with the aim of assessing the possible relationship between caffeine and behavioral symptoms in a large group of nursing home residents with dementia. The three-year study was embedded in the Elderly Care Physicians training program, and trainees collected data on caffeine consumption, cognition, behavioral symptoms and social status. The study design is described in detail in **chapter 4**. To the best of our knowledge, these efforts resulted in the largest existing dataset on cognition, behavior and caffeine consumption amongst nursing home residents. In **chapter 5** we discuss the results of a subgroup analysis of the persons with dementia. Just over 200 persons were included, of which 70% showed behavioral symptoms. People consuming low amounts of caffeine were most likely to have behavioral symptoms. Furthermore, some behavioral symptoms differed between persons with mild, moderate, moderately severe and severe dementia.

The **general discussion** starts with a closer look at the main target receptors of caffeine and the changing brain of a person with dementia. Subsequently, conclusions on the exploration of the relation between caffeine consumption and behavioral symptoms in persons with dementia are discussed in detail, including the clinical implications and considerations for further research.

In short, if one assumes that any association will have to be unidirectional and consistently linear, one might draw the conclusion that there is no relation between caffeine and behavioral symptoms in persons with dementia. However, this thesis provides data to support the argument that there is a complex relationship between caffeine and behavioral symptoms in persons with dementia, and this relationship differs per person, is dose-dependent, and changes with age and the presence of dementia. As caffeine consumption is an easy-to-manage intervention against the background of hard-to-manage behavioral symptoms that place a major burden on caregivers and reduce the quality of life of the person with dementia, it is advisable to include caffeine consumption in the vocabulary of the professional as a possible influencing factor.

Brief summary

As the number of patients suffering from dementia is still growing, most of the patients display behavioral symptoms at some time during the disease and these behavioral symptoms lower the quality of life and increase the burden of caregivers, adequate management of these symptoms is warranted. However, the etiology and management of behavioral symptoms is complex, resulting in (mis)use of pharmacological interventions: a cure which is often worse than the disease. In healthy adults, caffeine is known to influence behavior. Four different studies were conducted to see if caffeine is an easy to adjust cause or a pragmatic intervention for behavioral symptoms in patients with dementia. The first study found caffeine consumption to be correlated with less apathy, lower aberrant motor behavior and getting up at night. The second study found a reduction in caffeine consumption led to a decrease in behavioral symptoms (aggression, irritability, general restlessness and aberrant motor behavior) in one participant, but no difference in the other participant. A review of literature found few studies on the subject and some with severe methodological flaws, therefore no consistent conclusion on the relation between caffeine consumption and behavioral symptoms could be drawn. The last study showed behavioral symptoms (like agitation, disinhibition and depression) were most common in persons with low caffeine consumption. Based on these studies, we conclude caffeine can influence behavior in persons with dementia, but most likely not in all persons, not in all situations and not all of the time; but it can have an influence. In clinical practice it is advisable to consider caffeine as a possible moderator in the clinical assessment of behavioral symptoms in persons with dementia.

