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

Kromhout-Wegewijs, M.A.

G

GENERAL INTRODUCTION

The word "dementia" derives from the Latin stem 'demens' and literally means 'without mind.' Dementia syndrome is an umbrella term covering 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.(1) Alzheimer's disease is the most common cause of dementia, accounting for 60-70% of cases, but other common types of dementia include vascular dementia, Lewy body dementia and frontotemporal dementia. At present, around 50 million people worldwide have dementia and over the next 30 years this number is likely to triple.(2)

A simple question

Around ten years ago, when I was working as a physician at a nursing home, the multidisciplinary team was discussing a new resident in the dementia special care unit. She was showing agitated behavior in the evening and at night, but had never displayed this kind of behavior at home. Her behavior was analyzed in the multidisciplinary team meeting, including her (unmet) needs and possible physical or other contributing factors. The team then discussed treatment goals and options. Interestingly, the nurse mentioned an above average coffee consumption and asked whether the coffee could influence behavior. A simple question and one that couldn't be answered at that time, but this question has stayed with me ever since.

Dementia affects everyone differently and has a significant physical, psychological, and social impact. Several factors influence the quality of life of patients with dementia.(3, 4) Factors reflecting relationships, social engagement and functional ability are associated with an increase in quality of life(4), while poorer physical health (e.g. pain), mental health (including behavioral symptoms)(3, 4) and poorer caregiver well-being(4) are associated with a lower quality of life. The global economic costs of dementia are estimated to be around $1 trillion, including the cost of informal care(5), so dementia has a profound effect not only on the patient but also on caregivers and society as a whole. Enabling people with dementia and their caregivers to "live well" and maintain a good quality of life should be the main focus of policy and practice (e.g. the Dutch 'Waardigheid en Trots'(6) and the UK's 'Living well with dementia'(7)).

BEHAVIORAL SYMPTOMS IN PATIENTS WITH DEMENTIA

Behavior is referred to as 'an observable response to a concrete set of circumstances'. Patients with dementia display non-cognitive symptoms, e.g. aggression, agitation, anxiety, apathy, which are together referred to as behavioral symptoms. These symptoms are also often labeled as behavioral problems, behavioral disturbances, challenging behavior, behavioral and psychological symptoms of dementia (BPSD) or neuropsychiatric symptoms.

The etiology of behavior in patients with dementia is complex and improvements to the traditional medical model regarding the presentation of dementia has been suggested by Kitwood(8):

$$D = NI + H + B + P + SP$$

Kitwood proposed that the symptoms of dementia (D) can be understood as an interplay between neurological impairment (NI), psychosocial factors (health (H), individual psychology (P), biography (B)), and the environment (social context/psychology (SP). This proposal represented a rejection of the standard medical approach to dementia which focused on treating neurological impairments (D = NI). The enhanced model resulted in the Person-centered-care philosophy, which is the underlying philosophy of the 2018 Alzheimer's Association Dementia Care Practice Recommendations.(9) The application of this care philosophy benefits the person with dementia, for example in terms of improved quality of life, fewer behavioral symptoms, lower use of psychotropic medication and the maintenance of self-esteem, in addition to helping staff by improving working conditions.(9)

Almost all patients with dementia will show behavioral symptoms at some point during the disease(10) which decreases quality of life of the patient with dementia(3, 4) and place a high burden on informal caregivers. Due to the caregiver burden, behavioral symptoms are often the main reason for nursing home admission in patients with dementia.(11) Behavioral symptoms are also associated with a decline in general health and quality of life, and increased social isolation of the caregiver. 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 neuropsychiatric symptoms.(12) 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, (13) after which interventions can be formulated. Many different pharmacological treatments have been intensively studied. (14, 15) Although there is some evidence pharmacological agents (mainly cholinesterase inhibitors and atypical antipsychotics) can decrease behavioral symptoms in patients with dementia, the clinical effect is small and there are severe safety risks as study dropout, adverse effects and death.(14, 15) Psychosocial approaches have also been widely studied(16, 17) and 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(16, 18), a policy that is in line with the key components of person-centered care.(19) In view of these considerations, a stepped care approach is generally suggested as the best approach as it takes the different contribution factors and the individual context of the patient into account. However, even in the stepped care approach nutritional factors are not regularly included as a possible cause or intervention.

The management of behavioral symptoms in patients with dementia is complex and the burden for the patient and caregivers is high, often placing both caregivers and professionals at wits end. It is sadly no surprise that refuge is still regularly sought in pharmacological interventions, despite them being largely ineffective and potentially generating severe adverse effects. Therefore, fur-

ther research into the manageable causes and effective treatments of behavioral symptoms in dementia should be one of the focal points in elderly care.

CAFFEINE

Numerous anecdotes and mythological stories over the last 5,000 years(20) suggest that caffeine use can influence behavior, especially concerning a stimulatory effect that can relieve fatigue and improve mood. In early history people chewed the leaves or seeds, such as the Mate bush or the cocoa bean, releasing the caffeine. The infusions with boiling water that we now know as 'coffee' or 'tea' developed around 1000 AD(20), when it was discovered that boiling water enhanced the stimulatory effect. This discovery gave rise to our current use of coffee and tea, and drinking coffee and tea today has become more than a simple consumption of a stimulant, it is now a social event and a cultural habit. "Having a cup of coffee" or a "tea break" are today associated with socializing and relaxation.

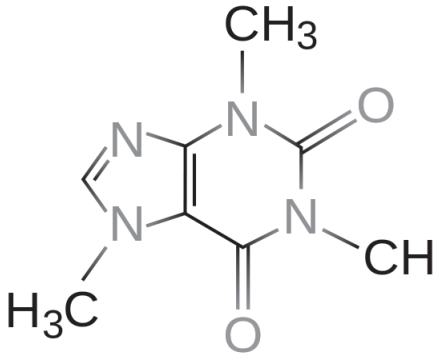

Figure 1. Chemical structure of caffeine (adjusted from https://commons.wikimedia.org/wiki/File:Caffeine.svg)

Figure 2. Coffee, the most common form of caffeine ingestion (source: Petr Kratochvil)

The Ethiopian myth of coffee
In the ancient coffee forests of the Ethiopian plateau, the goat herder Kaldi noticed that his goats became so energetic and agitated, seemingly even dancing, that they could not sleep at night after eating the berries of a certain bush. The goatherd tried the berries himself and reported his discovery to the abbot of the local monastery. From there knowledge of the energizing berries began to spread.

Caffeine is released when ground coffee beans contact hot water, and the longer the contact, the more caffeine is released. In 1819, the German chemist Friedrich Runge isolated pure caffeine from coffee, a discovery that later found application in the soft drinks industry, first by adding caffeine as a bitter seasoning to drinks such as Coca-Cola, Dr Pepper and Pepsi-Cola, and later by

adding caffeine specifically for its stimulatory effect (Xi and Red-Bull). The stimulatory effect of caffeine has also resulted in its use as an additive in certain medicines.

Pharmacologically, caffeine belongs to the alkaloids and is chemically related to nicotine, heroin and cocaine. With oral use, caffeine is absorbed by the body within about 30-60 minutes, and caffeine is then metabolized in the liver to three active metabolites: paraxanthine (approx. 80%), theophylline, and theobromine. In healthy adults, the half-life of caffeine is around 4.5 hours on average, but depends on factors such as age, medication use, liver function and smoking. In elderly people with severe hepatic impairment, the half-life of caffeine can increase to 96 hours (see table 1).

Table 1. Pharmacokinetics and pharmacodynamic effects of caffeine

Pharmacokinetic	Pharmacodynamic effects
• Rapidly and completely absorbed from the gastrointestinal tract or oral mucosa	• Non-selective antagonism of A2a and A1 adenosine receptors
• t_{max} 15-120 min, $t_{1/2}$ 2-8 hours	• Facilitates dopamine D2 receptor transmission
• Metabolization: by CYP1A2 in the liver to paraxanthine, theophylline and theobromine	• Tolerance can develop, attributed to the upregulation of adenosine receptors
• Variability in metabolism due to age, genetics (sex, CYP1A2 activity), smoking, medication use	• Tolerance can differ between organs
• Excreted in the urine	• Withdrawal symptoms 12-24h after ingestion

Caffeine is unique in that it is both water and fat soluble.(21) After ingestion caffeine can be found in all body fluids and can cross the blood-brain barrier, leading to a broad range of effects in the human body. General physical effects include but are not limited to: 1) Pain relief, 2) Increase in blood pressure, 3) A dose dependent effect on the heart rate (both bradycardia and tachycardia), 4) Other cardiac effects including arrhythmia, 5) Vasoconstriction that increases the risk of myocardial ischemia, 6) Delayed conception and decreased fertility (high caffeine consumption increases the risk of miscarriage), and 7) Increase in bladder instability.(22)

The effects of caffeine as a stimulant partly derive from the non-selective antagonism of adenosine receptors, especially the adenosine A2a receptors, the A1 receptors(23, 24) and the adenosine A2a receptor-dopamine D2 receptor heteromer.(23) In addition, caffeine also has a (weaker) affinity for benzodiazepine receptor sites and several studies have shown that caffeine can neutralize the effects of benzodiazepines.(24) Chronic consumption of caffeine likely increases the number of adenosine receptors but evidence for receptor regulation of the benzodiazepine receptor sites is conflicting.(24) Caffeine also influences the formation and release of other neurotransmitters such as acetylcholine, epinephrine, norepinephrine, serotonin, dopamine and glutamate.(24, 25)

CAFFEINE AND BEHAVIOR

As caffeine has been used for several centuries to influence behavior, unsurprisingly the effects of caffeine on behavior in adults have been widely researched. But, for many years the research into caffeine has been troubled by methodological challenges. In the early eighties a review(26) showed several weaknesses reoccurring frequently in caffeine research, namely: the use of weak hypothesis in experimental design, design flaws like excessive high dosages of caffeine, extrapolation of results from caffeine naïve to caffeine tolerant subjects and selective citation of literature. (Although the latter is a challenge for all research, not just caffeine research). A later review showed most studies still used a single high dosage of caffeine instead of the more realistic ingestion of several smaller dosages during the day.(27) Recently, the discussion of methodological challenges in caffeine research focused around confounding due to withdrawal symptoms, the use of caffeine naive participants and the question if these participants are a representative sample of the population and, lastly, the influence of tolerance.(28) It is essential to take these specific methodological challenges in caffeine research into account while interpreting literature, conducting research and choosing the best intervention for a specific patient.

Despite these methodological challenges in researching caffeine, it is now widely accepted that moderate caffeine consumption in healthy adults increases alertness,(27, 29, 30) attention (27, 29, 30) and cognitive function. (29, 30) It also elevates mood (30) and reduces fatigue (27). A high caffeine consumption (usually ≥ 300 mg) increases anxiety,(27, 30) can induce psychotic or manic symptoms (30) and impairs sleep (27). As these effects differ between individuals, people normally adjust their consumption of caffeine based on their personal experience of (non-)beneficial (side)effects.(27, 30)

In children, caffeine consumption has been linked to specific behavioral symptoms, including daytime sleepiness, anger and violent behavior, and an association between caffeine consumption and long-term behavioral symptoms has even been suggested by some.(22)

An exploration of existing literature produced three studies(31-33) on the effect of caffeine on behavioral symptoms in patients with dementia (prior to this thesis). Two of these studies, dating from the seventies(32) and the nineties(31), used evening administration of caffeine to examine the effect of caffeine on sleeping difficulties. The first study wanted to investigate a possible soporific effect of caffeine in patients with dementia, of which there was anecdotal evidence at the time. Twelve patients with Alzheimer's or Pick's disease with sleeping difficulties living in a nursing home were included. The participants were given caffeine beverages 30-45 min before bedtime in 4 different dosages (0-228mg), each dosage for 5 days followed by a 1-day wash-out period. No soporific effect of coffee was observed.(32) The second study was a 'reversed treatment trial'. After noticing a paradoxical effect of sedatives in patients with dementia often leading to a reversal of circadian rhythm according to the authors, they wanted to try the opposite: a stimulant in de evening and a sedative in the morning. For this study 16 patients with multi-infarct dementia and severe sleeping difficulties with a complete reversal of circadian rhythm were given

caffeine at 8pm and a sedative during the day. With this treatment 10 patients showed improvements in their circadian rhythm. The authors concluded that caffeine restores a normal sleep rhythm in patients with dementia.(31)

The third study,(33) a randomized controlled trial, examined the effect of 'coffee therapy' on behavioral symptoms measured with the Neuropsychiatric Inventory (NPI). In groups of 7-8 patients with dementia were welcomed into the room of a coffee shop by a master wearing a gown, an apron and a cap. Fresh coffee was grinded by the patients, after which filter coffee was made, sweetened and served in a china cup with saucer. Every patient was called by their name when receiving the coffee, and again when receiving a cracker. The coffee therapy was concluded with a chat, the reading of a poem or a story and was given twice a week for four weeks. The intervention group showed a significant decrease in NPI. However, the authors mention they administered several factors together (coffee, sugar and the situation of the coffee therapy itself) to create a most pleasant feeling and can determine which was the most effective factor.(33)

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.

HYPOTHESES

Based on the known stimulatory effects of caffeine in healthy adults, it seems logical to assume that, in patients with dementia, caffeine increases behavioral symptoms caused by general restlessness, anger and anxiety and increases sleeping difficulties during the night by suppressing fatigue. In healthy adults, insufficient rest at night leads to increased sleepiness during the day, which may in turn lead to increased caffeine use. However, in the absence of this self-compensating mechanism in patients with dementia, sleeping difficulties can lead to greater daytime sleepiness and a reversion of circadian rhythm which in its turn can also increase behavioral symptoms (e.g. irritability).

The opposite can also be hypothesized: certain behavioral symptoms in patients with dementia can be reduced by the use of caffeine. Although the etiology of behavioral symptoms is multifactorial and complex,(13) factors known to induce behavioral symptoms include overstimulation (comparable to patients suffering from autism) and incomprehension of a situation.(34) 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. Social activities in general can reduce behavioral symptoms in patients with dementia, (34) and a social gathering associated with coffee drinking might positively influence the behavior of patients with dementia.

To summarize, in theory caffeine consumption by patients with dementia could result in both an increase and a decrease in behavioral symptoms. The increase would be most likely seen in anxiety, general restlessness, anger and sleeping difficulties. Behavioral symptoms logical to decrease are those caused by overstimulation and incomprehension, which both can lead to a wide range of behavior. Both hypothesis were considered equally strong, therefore the aim of these studies 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.

DESIGN

In designing the study several of the known methodological challenges in caffeine research as well as known difficulties in behavioral research and research in elderly care were considered:

- Several modern caffeine studies work with caffeine naïve participants or animals, which makes extrapolation to caffeine tolerant patients unreliable. As coffee (and caffeine) is a widely and regularly consumed beverage, caffeine naive patients are the minority and most patients have (some amount of) caffeine tolerance. Therefore, the study population should resemble normal caffeine consumption so reliable extrapolations could be made.
- Frail elderly persons are frequently excluded from studies due to age or comorbidity leading to a severe underrepresentation in scientific research. Just like in any other area of medical research, to advance treatment and care continuously improving and offering new insights are necessary. For this reason the studies have to be pragmatic, excluding as little as patients as possible and conducted as much as possible in normal care situations.
- Caffeine can be seen as a possible cause of behavioral symptoms or an intervention, both asking for different kind of designs. As caffeine is consumed regularly by elderly patients with dementia, it was first seen as a possible cause of behavioral symptoms. If a relation between behavioral symptoms and caffeine consumption is likely, then possible intervention studies could be done.
- Earlies studies used (extremely) high dosages of caffeine. If we want to do justice to the three challenges mentioned above, our conclusions should be based on normal caffeine use (no injections or capsules) and normal caffeine dosages (no add ons).

These considerations lead to a stepwise research design consisting of four different studies. The first step were two different exploratory studies to see if there was some validation in the hypotheses. If these studies showed signs of a relation indicating the need for more thorough research, the following steps would be a systematic literature review and a large multicenter study using more research facilities.

First, an observational pilot study 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) questionnaire and a sleep questionnaire, together with careful observation of caffeine consumption in 29 patients with dementia (Chapter 1). Because caffeine shows strong individual variation in effects in healthy adults, a second exploratory study designed to examine the individual effects of caffeine on behavioral symptoms was performed. In two patients with high caffeine use and severe behavioral symptoms, caffeine consumption was regulated over a four-week period by serving either caffeinated or decaffeinated coffee. Behavioral symptoms were then scored using the NPI-NH and the Cohan Mansfield Agitation Inventory (CMAI), with outcomes individualized per patient. (Chapter 2)

The results of the two exploratory studies indicated further research was warranted. Hence, a thorough and systematic literature review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines, with the research question 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 and gray literature were searched and more than 4000 articles were screened for relevance, resulting in the identification of only seven relevant articles. (Chapter 3)

The final study, a large multicenter cohort study, was conducted with the aim of assessing a possible relationship between caffeine and behavioral symptoms in older nursing home patients with dementia, and if confirmed, to further assess contributory factors including the severity of dementia. The three-year study was embedded in the Elderly Care Physicians training program, and trainees collected data on caffeine consumption, cognition, behavioral symptoms (the NP-NH, the AES-C and MDS depression) and social information. To the best of our knowledge, these efforts resulted in the largest existing dataset on cognition, behavior and caffeine consumption amongst nursing home residents (Design: chapter 4; Results: chapter 5).

Lastly, in the ‘General discussion’ the overall results of the studies will be discussed to answer the simple clinical question “can coffee influence behavior in patients with dementia”.

Introduction – in short

As the number of patients suffering from dementia are still growing, most of the patients experience a kind of 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 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.

REFERENCES

1. Association AP. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.2013.
2. WHO. Factsheet Dementia 2017 [Available from: http://www.who.int/news-room/fact-sheets/detail/dementia.
3. Klapwijk MS, Caljouw MA, Pieper MJ, van der Steen JT, Achterberg WP. Characteristics Associated with Quality of Life in Long-Term Care Residents with Dementia: A Cross-Sectional Study. Dement Geriatr Cogn Disord. 2016;42(3-4):186-97.
4. Martyr A, Nelis SM, Quinn C, Wu YT, Lamont RA, Henderson C, et al. Living well with dementia: a systematic review and correlational meta-analysis of factors associated with quality of life, well-being and life satisfaction in people with dementia. Psychol Med. 2018;48(13):2130-9.
5. Xu J, Zhang Y, Qiu C, Cheng F. Global and regional economic costs of dementia: a systematic review. The Lancet. 2017;390:S47.
6. VWS. Waardigheid en trots. Liefdevolle zorg voor onze ouderen. . https://www.rijksoverheid.nl/documenten/rapporten/2015/02/10/waardigheid-en-trots-liefdevolle-zorg-voor-onze-ouderen; 2015.
7. Health Do. Living well with dementia: A National Dementia Strategy. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/168220/dh_094051.pdf; 2009.
8. Kitwood TM. Dementia Reconsidered: The Person Comes First: Open University Press; 1997.
9. Fazio S, Pace D, Flinner J, Kallmyer B. The Fundamentals of Person-Centered Care for Individuals With Dementia. Gerontologist. 2018;58(suppl_1):S10-S9.
10. Zuidema SU, Derksen E, Verhey FR, Koopmans RT. Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. International journal of geriatric psychiatry. 2007;22(7):632-8.
11. Borsje P, Hems MA, Lucassen PL, Bor H, Koopmans RT, Pot AM. Psychological distress in informal caregivers of patients with dementia in primary care: course and determinants. Family practice. 2016;33(4):374-81.
12. Isik AT, Soysal P, Solmi M, Veronese N. Bidirectional relationship between caregiver burden and neuropsychiatric symptoms in patients with Alzheimer's disease: A narrative review. International journal of geriatric psychiatry. 2019;34(9):1326-34.
13. Zuidema SU SM, Bil WME, Geelen R, Kok RM, Luijendijk HJ, van der Stelt I, van Strien AM, Vink MT, Vreeken HL. Multidisciplinary Guideline problem behaviour in dementia. Verenso, NIP. Utrecht 2018.
14. Seitz DP, Gill SS, Herrmann N, Brisbin S, Rapoport MJ, Rines J, et al. Pharmacological treatments for neuropsychiatric symptoms of dementia in long-term care: a systematic review. Int Psychogeriatr. 2013;25(2):185-203.
15. Wang J, Yu JT, Wang HF, Meng XF, Wang C, Tan CC, et al. Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2015;86(1):101-9.
16. Van Mierlo LD, Van der Roest HG, Meiland FJ, Droes RM. Personalized dementia care: proven effectiveness of psychosocial interventions in subgroups. Ageing Res Rev. 2010;9(2):163-83.
17. Vernooij-Dassen M, Vasse E, Zuidema S, Cohen-Mansfield J, Moyle W. Psychosocial interventions for dementia patients in long-term care. Int Psychogeriatr. 2010;22(7):1121-8.
18. van der Putten MJ, Wetzels RB, Bor H, Zuidema SU, Koopmans RT. Antipsychotic drug prescription rates among Dutch nursing homes: the influence of patient characteristics and the dementia special care unit. Aging Ment Health. 2014;18(7):828-32.

19. Brooker D. What is person-centered care in dementia? Reviews in Clinical Gerontlology. 2003;13(03):215-22.
20. Fredholm BB. Notes on the history of caffeine use. Handb Exp Pharmacol. 2011(200):1-9.
21. McCall AL, Millington WR, Wurtman RJ. Blood-brain barrier transport of caffeine: dose-related restriction of adenine transport. Life Sci. 1982;31(24):2709-15.
22. Temple JL, Bernard C, Lipshultz SE, Czachor JD, Westphal JA, Mestre MA. The Safety of Ingested Caffeine: A Comprehensive Review. Frontiers in psychiatry. 2017;8:80.
23. Ferre S, Diaz-Rios M, Salamone JD, Prediger RD. New Developments on the Adenosine Mechanisms of the Central Effects of Caffeine and Their Implications for Neuropsychiatric Disorders. J Caffeine Adenosine Res. 2018;8(4):121-31.
24. Nehlig A, Daval JL, Debry G. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. Brain Res Brain Res Rev. 1992;17(2):139-70.
25. Pohanka M, Dobes P. Caffeine inhibits acetylcholinesterase, but not butyrylcholinesterase. Int J Mol Sci. 2013;14(5):9873-82.
26. Grossman EM. Some methodological issues in the conduct of caffeine research. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association. 1984;22(3):245-9.
27. Smith A. Effects of caffeine on human behavior. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association. 2002;40(9):1243-55.
28. James JE. Caffeine and cognitive performance: persistent methodological challenges in caffeine research. Pharmacol Biochem Behav. 2014;124:117-22.
29. Einother SJ, Giesbrecht T. Caffeine as an attention enhancer: reviewing existing assumptions. Psychopharmacology. 2013;225(2):251-74.
30. Lara DR. Caffeine, mental health, and psychiatric disorders. J Alzheimers Dis. 2010;20 Suppl 1:S239-S48.
31. Domzal T. [Sleep disturbances in multi-infarction dementia and trials of treatment with caffeine]. Neurologia i neurochirurgia polska. 1990;24(3-4):133-8.
32. Ginsburg R, Weintraub M. Caffeine in the "sundown syndrome." Report of negative results. Journal of gerontology. 1976;31(4):419-20.
33. Matsuda H, Konno S, Satoh M, Sai H, Fujii M, Sasaki H. Coffee therapy for patients with behavioral and psychological symptoms of dementia. Geriatrics & gerontology international. 2012;12(3):568-70.
34. Alzheimer'sSociety. Changes in behaviour (factsheet 525LP). 2017.