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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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CAFFEINE AND NEUROPSYCHIATRIC SYMPTOMS IN PATIENTS WITH DEMENTIA: A SYSTEMATIC REVIEW

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ABSTRACT

Background:

The consumption of caffeine has well known effects on the behavior and sleep of healthy adults. Behavioral symptoms and sleeping difficulties are common in patients with dementia which may be affected by caffeine consumption. This systematic review examines the association between caffeine intake and neuropsychiatric symptoms in patients with dementia.

Methods:

In January 2019 an extensive search was conducted in Medline (PubMed), Embase, Emcare, Cochrane, PsychInfo, Web of Science and gray literature. Studies were included when they: i) investigated patients diagnosed with dementia, ii) reported neuropsychiatric symptoms, iii) used caffeine or coffee consumption as an intervention, and iv) reported associations between caffeine or coffee consumption and neuropsychiatric symptoms. Studies were excluded when they also included participants *without* a diagnosis of dementia, or presented a review or expert opinion. Two reviewers independently rated the studies and reached consensus on the appraisal.

Results:

Of the seven studies eligible for this review, four reported on sleeping difficulties and five on behavioral symptoms. There was no consistent effect of caffeine administration on neuropsychiatric symptoms: e.g., both high caffeine consumption and eliminating caffeine were associated with less apathy, the total Neuropsychiatric Inventory (Nursing Home) decreased after both coffee therapy and after eliminating caffeine, and both caffeine consumption and eliminating caffeine improved sleep.

Conclusion:

These findings suggest that caffeine can either induce or reduce neuropsychiatric symptoms in individual patients with dementia. Therefore, in these patients, caffeine consumption requires a prudent individualized approach and further research on the effects of caffeine on individual neuropsychiatric symptoms is required.

INTRODUCTION

In 2018 around 50 million people worldwide were reported to have dementia, with considerable impact on the patients and their caregivers.(1) Neuropsychiatric symptoms (e.g. aggression, agitation, anxiety, depression) are common in patients with dementia(2, 3) and lower the quality of life of both patients (4) and their caregivers.(5) Moreover, the etiology of these symptoms is complex and thought to be multifactorial, requiring detailed analysis of the contributory factors, followed by stepwise, tailored interventions.

In some guidelines on problematic behavior in dementia, caffeine is mentioned as a possible contributing factor in agitated behavior during the night (6) and, in healthy adults, is known to have physical effects on the body (e.g. increased diuresis) and influence behavior. For example, normal caffeine consumption in healthy adults increases alertness,(7-10) attention(7, 8, 10) and cognitive function,(7, 8) and elevates mood(8, 11) and reduces fatigue.(10) In higher dosages (usually ≥ 300 mg) caffeine may increase anxiety,(8, 10, 12) and induce psychotic or manic symptoms.(8) Caffeine intake prolongs sleep latency,(10, 12, 13) reduces sleep duration,(10, 12, 13) sleep efficiency(13) and fatigue(8), and also reduces subjective quality of sleep.(13) In adults, the effects of caffeine on sleep are dose and time dependent.(10, 13) The effect of caffeine on sleep and behavior in *older* persons is less well investigated. However, both older people and individuals with mental health problems may be more sensitive to caffeine compared to younger adults. (13) This places older people with dementia at potentially higher risk for an adverse influence of caffeine on behavior and sleep.

In view of the clear effects of caffeine on behavior and sleep in adults and the prevalence of neuropsychiatric symptoms in older patients with dementia, we hypothesized that there would be a correlation between caffeine intake and neuropsychiatric symptoms in patients with dementia. Therefore, this review examines the association between caffeine and neuropsychiatric symptoms in older patients with dementia.

METHODS

Search strategy

This systematic review was designed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.(14, 15) Details of the protocol were registered at PROSPERO and can be assessed at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018094098.

In January 2019 the following databases were searched: Medline (PubMed), Embase, Emcare, Cochrane, PsychInfo and Web of Science. At the same time, a second search was conducted in the gray literature: GLIN, Greylit, AACN Research & Data center, WHO, OpenGray, HSO and Clinicaltrials.gov. Moreover, all references of eligible articles were scrutinized for potential ad-

ditional studies. The search strategy was designed by the authors in collaboration with a medical information specialist.

Selection

Two reviewers (MK and NRO) independently conducted the search and assessed the relevance of each article. The reviewers compared the articles and reached consensus on the final eligibility of each article. Another independent reviewer was available if consensus was not reached; however, involvement of a third reviewer was not required.

Studies were included when they: i) included patients diagnosed with dementia, ii) reported neuropsychiatric symptoms, preferably using a valid scale or index: e.g. the Neuropsychiatric Inventory (NPI) (16) or the Cohen-Mansfield Agitation Inventory (17), iii) included caffeine or coffee consumption as an intervention, and iv) reported associations between caffeine or coffee consumption and neuropsychiatric symptoms.

Studies were excluded when they also included participants *without* a diagnosis of dementia, or presented a review or expert opinion.

Data extraction

One reviewer (MK) extracted the following data: study characteristics (authors, year of publication, country, study design, inclusion/exclusion criteria), patient characteristics (number, mean age, sex, type of dementia), caffeine, neuropsychiatric symptoms (scale/index used, results), associations between caffeine and neuropsychiatric symptoms, adjustments made for confounding/risk of bias, and funding. The data extraction was checked by a second reviewer (NRO).

Appraisal

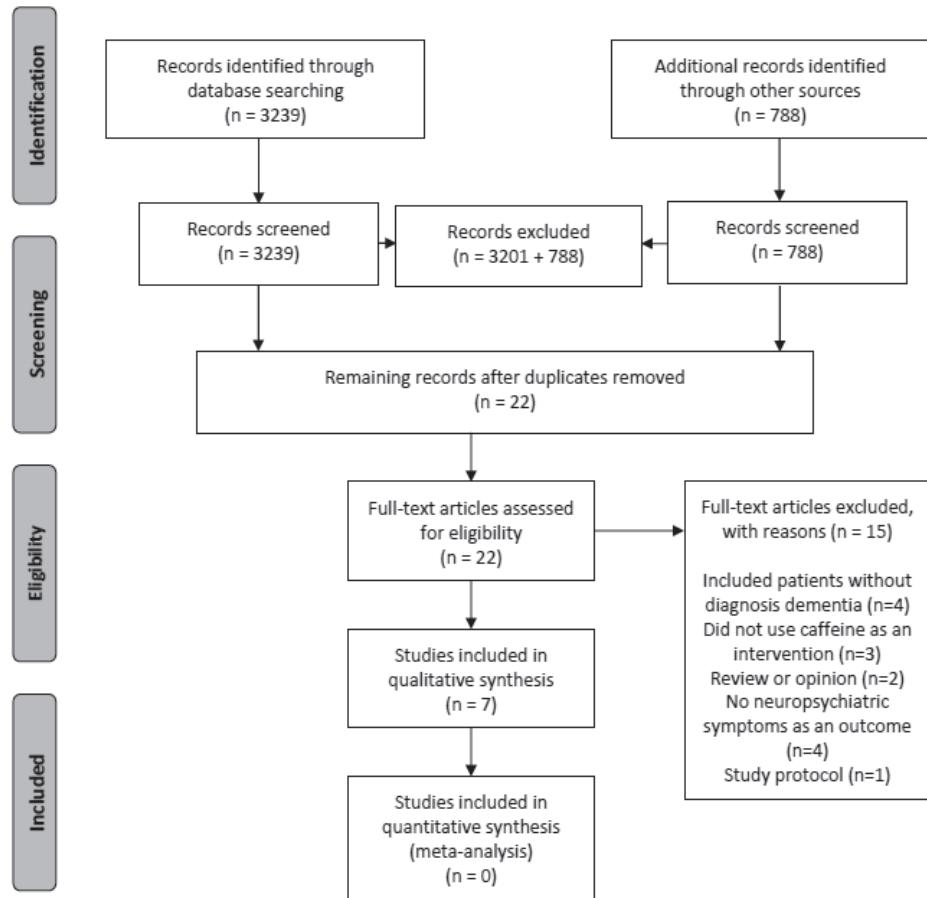
Since this review included mixed method studies, the Mixed Methods Appraisal Tool (MMAT) was used during the appraisal stage. The MMAT has been designed to assess the methodological quality of studies included in a systematic mixed studies review. The MMAT consists of two screening questions and five sections of specific questions regarding study type, e.g. qualitative, quantitative randomized controlled trial (RCT), quantitative non-RCT, quantitative descriptive, and mixed methods. For a mixed methods study three sections were used, i.e. the qualitative section to appraise the qualitative component, the appropriate section for the quantitative component, and the mixed methods section. For all types of studies, an overall quality score was calculated to indicate methodological quality.(18) Two reviewers (MK and NRO) independently assessed the studies and reached consensus on the scoring metrics. However, since one of the reviewers (MK) co-authored two of the included studies, in the assessment of these latter studies MK was replaced by the third reviewer (EJG).

RESULTS

Search results

The primary search resulted in 3,239 potentially relevant articles; after screening for eligibility, only 7 studies remained. The secondary search yielded 788 potentially relevant articles, of which none met the inclusion criteria (Fig. 1).

Figure 1: flowchart



Study characteristics

The seven included studies differed in almost all aspects, including: i) study type (from a case report(19) to a RCT(20)), ii) publication date (ranging from 1976 (21) to 2018 (22)), and iii) methodology (qualitative and quantitative). However, all studies included patients with some type of dementia.

One study excluded patients with certain types of dementia.(21) In five studies caffeine was regulated,(20-24) one study observed caffeine consumption(25) and one used self-reported consumption.(19) Three studies measured behavioral problems,(19, 20, 24) two studies reported on sleeping difficulties(21, 23) and two studies reported on both.(22, 25) Characteristics of the included studies are presented in Tables 1 and 2.

Appraisal

The one quantitative RCT, and the one mixed method and five quantitative non-RCTs were scored using the MMAT criteria. The mixed method study(21) scored lowest (0%), mainly due to the qualitative part of the study in which none of the MMAT criteria were met. The oldest quantitative non-RCT(23) lost points (MMAT score 25%) due to unclear selection, inappropriate measurements, and the absence of control persons. Three studies scored 50% on the MMAT.(19, 22, 24) The qualitative case report did not analyze the data and did not consider the influence of the researchers.(19) In the two single-subject trials (both reported in (24)), the participants were carefully selected and the article did not report complete outcome data. The most recent qualitative non-RCT also had incomplete outcome data and did not correct for possible confounders.(22) The other two studies met all the criteria for the appropriate study method.(20, 25) (Tables 1 and 2)

Caffeine or coffee consumption

In all studies, the investigated hypothesis was whether caffeine was a determinant for the reported neuropsychiatric symptoms. However, the way the caffeine was ingested ranged from injections,(23) caffeinated beverages,(20-22, 24, 25) medication,(19) to oral ingestion (not further specified).(23) The following were used as (de)caffeinated beverages: instant coffee, filter coffee, pour-over coffee, coffee from pads, black tea and cola.

The amount of caffeine in coffee varies according to the method used to make the coffee, e.g. filter coffee contains more caffeine than espresso due to the longer extraction time. Two studies mentioned the exact caffeine dosage,(21, 23) two made estimates based on the method of coffee making,(24, 25) and one study made an estimation based on self-reported medication use.(19) Since two trials did not mention caffeine dosage during the intervention (20, 22), an estimation was made (if possible) based on the information in the article. In the seven studies, caffeine consumption ranged from 0-300 mg/day, and was reported to be 1300 mg/day in the case report (Table 3).

Neuropsychiatric symptoms

Two trials,(20, 22) the two single-subject trials,(24) an observational study,(25) and the case report(19) assessed the relationship between caffeine and various behavioral symptoms. The included studies reported both positive and negative effects of caffeine on behavioral symptoms.

Table 1: Characteristics of the studies with sleep as outcome

Article	Study characteristics				Patient characteristics				
	Design	Inclusion criteria	Exclusion criteria	Setting	N	Age (yrs)	Sex (% F)	Type of dementia	
Ginsburg et al. 1976 USA ¹	Qualitative and quantitative double-blind trial	Medication resistant sleeping difficulties	Dementia by trauma, infection, metabolic or vascular diseases, intoxication, neoplasms or NPH	Nursing home	12	-	-	Alzheimer or Pick's disease	
Domzal. 1990 Poland	Reversed treatment non-randomized trial	-	-	Hospital	16	51-81	44	Multi-infarct dementia	
Kromhout et al. 2014 Netherlands	Observational study	All residents of a dementia special care unit	Psychiatric morbidity; terminal phase; no informed proxy consent	Nursing home	29	84 (69-96)	72	55% Alzheimer 14% VD 3% Mixed 3% Korsakoff 24% NOS	
de Pooter-Stijnman et al. 2018 Netherlands	Pre-post intervention trial	Diagnoses of dementia, at least 1 cup of coffee/day	No informed consent, life expectancy < 1 month or living < 4 weeks in the unit at start of the study	Nursing home	21	87 (70-98)	81	24% Alzheimer 19% VD 14% Mixed 5% FTD 38% NOS	

NPS: neuropsychiatric symptoms; MMAT: Mixed Methods Appraisal Tool; NPH: Normal pressure hydrocephalus;; CMAI: Cohen-Mansfield Agitation Inventory; AMB: aberrant motor behavior; F: female; VD: vascular dementia; FTD: frontotemporal dementia; NOS: dementia not otherwise specified

¹ Authors do not explicitly state the country of study, but both are affiliated with the University of Rochester, New York, USA.

² All non-significant results are also reported in the article.

³ More results reported in the article. None of the articles mention funding.

Caffeine	NPS -sleep Outcome and scale/ index used	Results	Conclusion	Adjustments made for confounding and bias	MMAT score
4 x 5 days separated by 1-day washout: 1. A hot liquid (0 mg) 2. Coffee (48mg) 3. Coffee (138mg) 4. Coffee (228mg) 30-45 min before bedtime	Sleep induction time; quality of sleep; total length of sleep; time wake during the night and a global sleep rating	N=3: increased sleep on 138 mg caffeine. No significant difference was found between the placebo and the 3 dose levels of caffeine.	No soporific effect of coffee in patients with dementia.	No hypnotics or tranquilizing medication the month before and during the trial	0%
Caffeine at 8 p.m.: 0.1-0.2 caffeine oral or per injection. Sedatives during the day.	Circadian rhythm sleep disorders	N=6: no change N=10: average 4 h improvement in sleep rhythm N=3: died	Caffeine restores the normal sleep rhythm.	-	25%
Consumption of coffee, tea and cola was recorded 8 times/day during 4 days. Average use: 15 units of caffeine (SD 5.6) per person during 4 days.	Sleep: if a patient got up at night and lay awake in bed or was asleep.	Total caffeine and getting up at night (KT 0.462 p<0.01). Evening caffeine and getting up at night (KT 0.436, p<0.01; ML b=0.48 (0.22), Wald (461) = 2.20, p=0.03). ²	Caffeine consumption is positively correlated with getting up at night.	All nursing and nutrition staff were trained in the use of the questionnaires. Multilevel analysis was used to correct for the nested structure of the data.	100%
3x2 weeks: 1. Baseline (pre-intervention). 2. Wash-out period (gradually reducing caffeine intake to intervention situation.) 3. Post-intervention (caffeinated coffee from 6 a.m. to 12 a.m. and decaffeinated coffee from 12 a.m.)	Sleep questionnaire: quietly sleeping, restlessly sleeping, quietly awake or restlessly awake. A total sleep score (good vs. poor sleep)	Quietly sleeping (pre 83%. post 87% p=0.032) The total sleep score improved significantly post-intervention compared to pre-intervention (p=0.015). ³	Eliminating caffeine in the afternoon and evening improves sleep.	Several possible confounders were noted, but not statistically corrected	50%

Table 2: Characteristics of studies with behavior as outcome.

Article	Study characteristics				Patient characteristics			
	Design	Inclusion criteria	Exclusion criteria	Setting	N	Age (yrs)	Sex (% F)	Type of dementia
Matsuda et al. 2012 Japan	Random-ized trial	-	-	Geriatric hospital	29	81 ± 8	66	Dementia (DSM-IV criteria)
Kromhout et al. 2014 Netherlands	Obser-vational study	All residents of a special care unit for dementia	Psychiatric morbidity; terminal phase; no informed proxy consent	Nursing home	29	84 (69- 96)	72	55% Alzheimer 14% VD 3% Mixed 3% Korsakoff 24% NOS
Golden et al. 2015 USA	Case report	-	-	ER and ICU	1	61	0	Dementia
Kromhout et al. 2017 Netherlands	Two double-blinded single-subject trials	Patients with a high intake of caffeine and severe NPS	Psychiatric morbidity; no informed proxy consent	Nursing home	2	85 -91	100	50% Alzheimer 50% Mixed
de Pooter-Stijnman et al. 2018 Netherlands	Pre-post intervention trial	Diagnoses of dementia, at least 1 cup coffee a day	No informed consent, life expectancy < 1 month or living < 4 weeks in the unit at start of the study	Nursing home	21	87 (70- 98)	81	24% Alzheimer 19% VD 14% Mixed 5% FTD 38% NOS

NPS: neuropsychiatric symptoms; MMAT: Mixed Methods Appraisal Tool; NPH: Normal pressure hydrocephalus; NPI(-NH): neuropsychiatric inventory (nursing home edition); CMAI: Cohen-Mansfield Agitation Inventory; AMB: ambulant motor behavior; F: female; ER: emergency room; ICU: intensive care unit; VD: vascular dementia; FTD: fronto-temporal dementia; NOS: dementia not otherwise specified

¹ All non-significant results are also reported in the article.

² More results reported in the article.

None of the articles mention funding.

Caffeine	NPS -behavior Outcome and scale/index used	Results	Conclusion	Adjustments made for confounding and bias	MMAT score
Coffee therapy (n=14) vs control therapy (n=15), 2/week for a month.	NPI	Intervention: NPI baseline 23 ±12, end 15 ±11 ($p<0.05$). Control: NPI baseline 22 ±13, vs 20 ±12.	Coffee therapy might be one of the non-medical treatments for NPS.	Outcome was measured blinded to treatment status.	100%
Consumption of coffee, tea and cola was recorded 8 times/day for 4 days. Average use: 15 units of caffeine (SD 5.6) pp in 4 days.	NPI-NH items agitation, depression, anxiety, apathy, irritability and AMB.	Total caffeine and apathy (KT -0.287 p=0.03; ML b=-0.88 (0.45) Wald (461) = -1.96, p=0.05); AMB (ML b= -0.47 (0.22) Wald (461)= -2.12, p=0.03). ¹	Caffeine consumption is negatively correlated with apathy and AMB.	All nursing and nutrition staff were trained in the use of the questionnaires. Multilevel analysis was used to correct for the nested structure of the data.	100%
BC Powder (845mg aspirin/ 65mg caffeine) 5-20 packets a day	-	-	Overuse of aspirin/ caffeine induced psychosis in this patient with dementia.	-	50%
4 weeks of regulated caffeine consumption using unrecognizable caffeinated or decaffeinated coffee pods.	NPI-NH and CMAI. Patient A: general restlessness, agitation and aggression. Patient B: anger and aggression.	A: NPS decreased in the decaffeinated weeks and increased slightly on reintroduction of regular coffee (NPI-NH agitation week 1 to 4 12, 3, 1, 4; CMAI general restlessness 6, 6, 1, 6.) ² B: no relationship.	NPS is influenced by caffeine in some patients with dementia.	Patients and staff were unaware of the predetermined order and blinded for the intervention. Patients were their own controls.	50%
3x2wks: 1. Pre-intervention. 2. Wash-out period (gradually reducing caffeine to intervention situation.) 3. Post-intervention (caffeinated coffee from 6 a.m. to 12 a.m. decaffeinated coffee from 12 a.m.)	NPI-NH items agitation, apathy, irritability and AMB	Apathy (pre 35% 1-2 post 10% 1 p=0.020). NPI-NH items agitation, irritability and AMB did not differ between pre-and post-intervention. ²	Eliminating caffeine in the afternoon and evening decreases apathy.	Several possible confounders were noted, but not statistically corrected	50%

Table 3: Caffeine consumption and results per study

Study	(Estimated) caffeine consumption (per day)	Result
Ginsburg	0mg – 48mg – 138mg – 228mg	In 3 patients increased sleep on 138mg
Domzal	0,1 – 0,2 caffeine (oral or per injection)	10 patients improved their duration of sleep
Matsuda	½ cup filter coffee 2/week Estimate: $85\text{mg}/2/7^*2 = 12\text{mg}$	NPI score on baseline 23, at the end 15
Kromhout 2014	Average use 15 units of caffeine pp in 4 days: $85\text{mg}^*15/4 = 319\text{mg}$	Negative correlation with apathy and AMB Positive correlation with getting up at night
Golden	5-20 packets a 65mg = 325 – 1300mg	Psychoses
Kromhout 2017	203mg – 43mg – 44mg – 169mg	Relation between specific NPS and caffeine consumption
Pooter	Baseline: mean 300mg (range 150-375) Intervention: no caffeine after 12 a.m.	Eliminating caffeine in the afternoon and evening decreases apathy and improves sleep.

The trial from Japan used the NPI to measure the difference in neuropsychiatric symptoms between coffee therapy and control therapy in a group of 29 patients with dementia.(20) Coffee therapy was described as a 30-min social activity in which fresh coffee was ground, brewed and served. Compared to the control group, the coffee therapy group had a significant drop in the total NPI score.(20) In one of the single-subject trials, a decrease in total Neuropsychiatric Inventory Nursing Home edition (NPI-NH) was seen during the decaffeinated period.(24) The other studies did not report the total NPI-NH score, but reported on specific NPI-NH items. In the observational study, a higher use of caffeine was associated with a lower score on the NPI-NH item 'apathy' and a higher score on 'aberrant motor behavior'.(25) Interestingly, the most recent study showed a decrease in 'apathy' after eliminating caffeine after 12 a.m. and no relation with 'aberrant motor behavior'.(22) One of the single-subject trials showed no effect of caffeine on behavior, whereas the other showed a negative effect of caffeine on several NPI-NH items (e.g. agitation/aggression) and on the NPI-NH psychomotor behavior cluster score.(24) The case report identified caffeine abuse, in combination with aspirin, as being the main cause of psychoses.(19)

Four studies reported on sleeping difficulties (Table 2). Caffeine was found to increase the number of times patients with dementia got out of bed (25) and eliminating caffeine increased the number of times patients with dementia were quietly sleeping and also improved the total sleep score,(22); these effects are similar to those reported in healthy adults. However, in contrast to the effects in healthy adults, in patients with dementia no relationship was found with sleep induction time,(21) quality of sleep,(21) time awake during the night(21, 25) and global sleep rating.(21) In two trials caffeine was administered in the evening, i.e. at 8 p.m. (23) or 30-45 min before bedtime(21). In both these studies some of the participants showed an improvement in sleep: 3 of 12 showed increased sleep on 138 mg of caffeine and 10 of 16 showed improvement in the circadian rhythm.

DISCUSSION

Although caffeine is widely used and its effects have been extensively studied in healthy adults, our comprehensive search yielded only seven small studies assessing the relation between caffeine consumption and neuropsychiatric symptoms in patients with dementia. Thus, the evidence is limited and most studies had methodological issues. Despite our thorough analysis of these studies, no consistent conclusions could be drawn regarding caffeine consumption and neuropsychiatric symptoms in patients with dementia. However, in each trial, the behavior of some participants seemed to be (strongly) influenced by caffeine consumption but in unpredictable ways, thereby emphasizing the need for an individualized approach.

The absence of a consistent effect might be due to the relatively normal dosage of caffeine used in the studies. In healthy adults, a chronic caffeine consumption of up to 400 mg a day is generally regarded as safe;(26, 27) in the case of caffeine abuse the daily dosage exceeded this level and resulted in psychosis.(19) Individuals who are sensitive to caffeine, pregnant women, and people with mental or psychiatric disorders and disabilities (e.g. individuals with dementia) might be more susceptible(28) and experience adverse effects at a much lower dosage. In the studies in the present review, this might be why some of the participants showed a change in behavior that was attributed to caffeine.

A second reason for the absence of a consistent effect might be the differences in study populations. Although all studies included patients with dementia, some of the studies included only patients with dementia and behavioral symptoms(Golden et al., 2015; Ginsburg and Weintraub, 1976; Kromhout et al., 2017). However, there was no consistent effect of caffeine on behavior in the studies that included only patients with dementia and behavioral symptoms, nor in the studies that included patients with dementia with and without behavioral symptoms. This suggests other factors contribute to the effect of caffeine on behavioral symptoms.

Another reason for the absence of a consistent effect might be the way that neuropsychiatric symptoms are reported. In the present review, with the exception of the case report, all studies used a version of the NPI to assess neuropsychiatric symptoms. The NPI consists of 12 neuropsychiatric symptoms (hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior, sleep and night-time behavior change, and appetite/eating change) of which the severity and frequency are rated and multiplied to create a symptom score.(16) The NPI implies that neuropsychiatric symptoms tap from one underlying latent variable construct, thus representing a single underlying disorder, where the level of severity is measured as a sum score. The questions in the NPI-NH have the same content as the questions of the NPI but have been rephrased for the nursing home population. (16, 29) Caffeine is known to have heterogeneous effects, potentially increasing several neuropsychiatric symptoms (e.g. agitation, anxiety, sleep disorders) and decreasing others (e.g. depression or apathy), both measured with the NPI(-NH). Therefore, a net neutral result could be based on the total NPI(-NH) score, whereas important insights might be derived by analyzing the

effects on neuropsychiatric symptoms in individual patients. This implies that larger studies are required on the effects of caffeine on individual neuropsychiatric symptoms.

In healthy adults, the negative effects of caffeine on sleep are thought to be caused by antagonizing the adenosine (A1 and A2) receptors in the brain.(13) Similar to the effects in healthy adults, caffeine was found to negatively impact sleep in some patients with dementia.(22, 25) However, surprisingly, in some patients the use of caffeine seemed to improve circadian rhythm(23) and sleep.(21) This positive effect of caffeine on sleep was also found in a 71-year-old man with a sleeping problem unresponsive to sedatives, who slept soundly after a cup of strong coffee before bedtime.(30) The author suggested that sleeping problems could have been caused by confusion. The consumed coffee could diminish the confusion by increasing attention and therefore have a positive effect on sleep. In the present review, no data were available on the amount of confusion of older patients with dementia who responded positively to caffeine,(21, 23); however, due to their illness, confusion might have played a role.

Another possible mechanism is the neurobiological changes in adenosine receptors, as A1 receptor density reduces and the A2 receptor expression increases during the progression of Alzheimer dementia.(31) The A1 receptor inhibits a cascade of effects which promote 'wakefulness', while the A2 receptor stimulates several mechanisms which induce 'sleepiness'.(32) By antagonizing both A1 and A2 receptors, caffeine impairs sleep. However, due to the different changes in receptor expression during disease progression, this effect might differ between healthy adults, patients with a mild dementia, and patients with severe Alzheimer dementia. In the treatment of dementia, the same paradox has been suggested, i.e. as in early dementia, an adenosine agonist might improve cognitive function and, as the disease progresses, adenosine antagonists have a more positive effect.(33) Therefore, caffeine may have a positive effect on sleep in patients with severe dementia, unless the diuretic effect of caffeine awakens them.

In adults, the effects of caffeine on behavior differ between individuals and can be influenced by genetics, expectations, frequency of use and tolerance developed. Generally, if there are effects, the individual regulates their caffeine consumption to minimize the adverse effects (12) or maximize the positive effects.(10) However, patients with dementia (especially institutionalized patients) cannot always modulate their caffeine consumption for their own benefit. Therefore, caretakers need to know the prior caffeine use/preferences of their patients and, in the case of behavioral symptoms, actively assess whether these might be attributable to caffeine use. However, this may not be easy and involves considering that something as common as caffeine (often used on a daily basis) can have both a positive or negative impact on complex behavior and neuropsychiatric symptoms in patients with dementia.

CONCLUSION

This systematic review found no consistent effect of caffeine administration on neuropsychiatric symptoms in patients with dementia. Further research on the effects of caffeine on individual neuropsychiatric symptoms in patients with dementia is therefore warranted. However, there were indications that caffeine can both induce and reduce neuropsychiatric symptoms and sleeping difficulties in individual patients with dementia. Since ingestion of caffeine is an easily adaptable intervention, it is recommended to include caffeine consumption in the individualized approach of neuropsychiatric symptoms in patients with dementia.

REFERENCES

1. WHO. Factsheet Dementia 2017 [Available from: <http://www.who.int/news-room/fact-sheets/detail/dementia>].
2. Zuidema SU, Derkx 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.
3. Zuidema SU, van der Meer MM, Pennings GA, Koopmans RT. [Prevalence of behavioural problems in a group of demented nursing home patients]. Tijdschrift voor gerontologie en geriatrie. 2006;37(1):19-24.
4. van de Ven-Vakhteva J, Bor H, Wetzel RB, Koopmans RT, Zuidema SU. The impact of antipsychotics and neuropsychiatric symptoms on the quality of life of people with dementia living in nursing homes. International journal of geriatric psychiatry. 2013;28(5):530-8.
5. 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.
6. Zuidema SU, Smalbrugge M, Bil WME, Geelen R, Kok RM, Luijendijk HJ, et al. Multidisciplinary Guideline problem behaviour in dementia. Utrecht: Verenso, NIP; 2018.
7. Einother SJ, Giesbrecht T. Caffeine as an attention enhancer: reviewing existing assumptions. Psychopharmacology. 2013;225(2):251-74.
8. Lara DR. Caffeine, mental health, and psychiatric disorders. Journal of Alzheimer's disease : JAD. 2010;20 Suppl 1:S239-48.
9. Massey LK. Caffeine and the elderly. Drugs & aging. 1998;13(1):43-50.
10. 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.
11. Grossi G, Micek A, Castellano S, Pajak A, Galvano F. Coffee, tea, caffeine and risk of depression: A systematic review and dose-response meta-analysis of observational studies. Molecular nutrition & food research. 2016;60(1):223-34.
12. Nawrot P, Jordan S, Eastwood J, Rotstein J, Hugenholtz A, Feeley M. Effects of caffeine on human health. Food additives and contaminants. 2003;20(1):1-30.
13. Clark I, Landolt HP. Coffee, caffeine, and sleep: A systematic review of epidemiological studies and randomized controlled trials. Sleep medicine reviews. 2017;31:70-8.
14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine. 2009;6(7):e1000100.
15. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ (Clinical research ed). 2015;350:g7647.
16. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308-14.
17. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. Journal of gerontology. 1989;44(3):M77-84.
18. Pluye P, Robert E, Cargo M, Bartlett G, O'Cathain A, Griffiths F, et al. Proposal: A mixed methods appraisal tool for systematic mixed studies reviews. 2011 [Available from: <http://mixedmethodsappraisaltoolpublic.pbworks.com>].

19. Golden LE, Sasoon P, Caceda R. A case report of late onset psychosis with dementia and aspirin and caffeine addiction. *Schizophrenia research*. 2015;168(1-2):591-2.
20. 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.
21. Ginsburg R, Weintraub M. Caffeine in the "sundown syndrome." Report of negative results. *Journal of gerontology*. 1976;31(4):419-20.
22. de Pooter-Stijnman LMM, Vrijkotte S, Smalbrugge M. Effect of caffeine on sleep and behaviour in nursing home residents with dementia. *European Geriatric Medicine*.
23. Domzal T. [Sleep disturbances in multi-infarction dementia and trials of treatment with caffeine]. *Neurologia i neurochirurgia polska*. 1990;24(3-4):133-8.
24. Kromhout MA, Numans ME, Achterberg WP. Reducing behavioral symptoms in older patients with dementia by regulating caffeine consumption: Two single-subject trials.. *European Geriatric Medicine* 2017;8:496-8
25. Kromhout MA, Jongerling J, Achterberg WP. Relation between caffeine and behavioral symptoms in elderly patients with dementia: an observational study. *The journal of nutrition, health & aging*. 2014;18(4):407-10.
26. Breedveld BC, Peters JAC. Cafeine factsheet: Voedingscentrum; [Available from: <https://mobil.voedingscentrum.nl/Assets/Uploads/voedingscentrum/Documents/Professionals/Voedselvoorlichting/Factsheets/Factsheet%20Cafeïne.pdf>].
27. U.S. Department of Health and Human Services. Dietary guidelines for Americans, 2015-2020. 2015 [Available from: <https://health.gov/dietaryguidelines/2015/guidelines/>].
28. 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.
29. Wood S, Cummings JL, Hsu MA, Barclay T, Wheatley MV, Yarema KT, et al. The use of the neuropsychiatric inventory in nursing home residents. Characterization and measurement. *Am J Geriatr Psychiatry*. 2000;8(1):75-83.
30. Hare RB. Sleep in the elderly. *Canadian Medical Association journal*. 1968;98(3):176.
31. Rahman A. The role of adenosine in Alzheimer's disease. *Current neuropharmacology*. 2009;7(3):207-16.
32. Bjorness TE, Greene RW. Adenosine and sleep. *Current neuropharmacology*. 2009;7(3):238-45.
33. Marzagalli R, Castorina A. The seeming paradox of adenosine receptors as targets for the treatment of Alzheimer's disease: agonists or antagonists? *Neural regeneration research*. 2015;10(2):205-7.