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NON-PHARMACOLOGICAL INTERVENTIONS FOR SLEEPING DISORDERS IN PATIENTS WITH DEMENTIA

Dimitriou Tatiana-Danai* PhD Student, Neuroscience Department, Aristotle University Of Thessaloniki Faculty Of Medicine, Greece *Corresponding Author

Verykouki Eleni PhD, Laboratory of Hygiene, School of Medicine, Aristotle University of Thessaloniki, Greece

Papatriantafyllou John Psychiatrist, PhD, 3rd Age Center IASIS, 2nd Neurology dpt., University of Athens, 'Attikon' Hospital, 73 Krimeas str., Glyfada Athens, Greece

Konsta Anastasia Assist. Professor, 1st Department of Psychiatry, "Papageorgiou" General Hospital of Thessaloniki, Aristotle University of Thessaloniki, Greece.

Kazis Dimitrios Assistant Prof in Neurology, 3rd Neurology Department Aristotle University of Thessaloníki.

Tsolaki Magdalini Neuropsychiatrist, Professor, 3rd Department of Neurology, Aristotle, University of Thessaloniki, Makedonia, Greece

ABSTRACT

BACKGROUND: Dementia is a devastating neurodegenerative disease that affects 47.5 million people globally. The Behavioural and Psychological Symptoms of Dementia (BPSD) affect patients with dementia (PwD) from MCI to severe stage of the disease. Sleeping disturbances, one of BPSD symptoms, include night-time awakenings, daytime sleepiness, insomnia and nightmares. The pharmacological approach have side effects that should be taken under serious attention.. The non-pharmacological management aims to improve the quality and quantity of sleep.

METHODS/ DESIGN: The trial is a cross-over randomized controlled trial (RCT) conducted in Greece. Sixty (60) participants with all types and stages of dementia were randomly assigned to 6 different groups.

DISCUSSION: The most effective non-pharmacological intervention for the sleeping disturbances in PwD was "psychoeducational programme for the caregivers- structured bedtime routine". The second more effective was "physical exercise" and the third was "aromatherapy and massage therapy". The literature so far lacks of large single or double-blinded randomized controlled trials.

1. INTRODUCTION

Dementia is a devastating neurodegenerative disease which affects initially the cognitive abilities of the patients and causes, while it progresses, functional, behavioural and psychological symptoms (BPSD). The BPSD are a crucial matter of dementia because studies have shown that affect the 98% of the PwD in moderate and severe stages[1]. The presence of these BPSD has been shown to increase caregiver's depression, burden and anxiety levels and may also cause other physical and psychological problems[2].

Specifically, sleeping problems are commonly present in dementia. It is a crucial disorder because frequently leads PwD to nursing homes[3]. The pharmacological treatment of sleeping disturbances includes drugs such as; melatonin and z-hypnotics. Benzodiazepines are usually avoided because of their side effects and cholinesterase inhibitors are used for the treatment of Alzheimer's disease, though can also improve sleeping problems. However, the side effects should be well considered[4].

Therefore, the present study aims to access three non-pharmacological interventions that can improve the sleeping disorders in PwD. To achieve this, we designed a cross randomized trial.

2. MATERIALS AND METHODS

2.1. Subjects

In this study, we included sixty patients from the Neurological Department of the General Hospital of Athens, Greece "G. Gennimatas". The patients were diagnosed all stages and types of dementia (AD, CardioVascular Dementia, Lewy Body Dementia, Frontotemporal Degeneration, MCI, Mixed Type AD & CVD and Aids).

Table 1 shows demographic data and baseline measures. Forty eight and three (48,3%) in this study were women, with average age 74,3 years old (Mean, 74.3; SD 8.6). Their average years of education were 9.9 (Mean 9.9; SD 4.5).

2.2 Procedure

This is a randomized, controlled, crossover trial. The NPI inventory applied to the family caregivers before any treatment and guidelines. The patients were randomly followed in six different groups, as in table A below;

Table A shows the sequence of the procedure

Group	Sequence	1st week	2st week	3st week
1	ABC	A	B	C
2	ACB	A	C	B
3	BAC	B	A	C
4	BCA	B	C	A
5	CAB	C	A	B
6	CBA	C	B	A

We were keeping records at the beginning and end of every intervention.

2.3 Interventions

Psychoeducational Programme for the Caregivers: Structured Bedtime Routine

Our psychoeducational programme for the caregivers aimed to educate them about dementia, BPSD and other matters related to the disease. The programme took place in face to face meetings in the General Hospital of Athens "G. Gennimatas" and in online meetings in collaboration with the ASPAD programme of Aristotle University, Thessaloniki. The programme included 24 seminars, lasted for 12 weeks and the duration of the seminar was approximately 2 hours. Although the literature so far lacks of evidence for the "structured bedtime routine", however there are

some trials that mention that this kind of intervention as effective[5,6].

Our intervention was administrated accordingly to the daily programme of every family caregiver. Most family caregivers chose a specific time at night to put in bed their patients and also to provide them with 8 hours night sleep. The psychoeducational programmes for the caregivers seem to be effective and have promising results[7,8].

Aromatherapy and Massage therapy
Aromatherapy in combination with massage therapy has shown promising results on the sleeping disturbances in PwD. Nevertheless, the mechanisms of action of aromatherapy are yet unknown[9], however lavender oil, melissa- based and lemon balm oil have been reported with anti-oxidant actions of vitamin E, which improves the state of blood vessels close to the skin and that is why there are the most common used oils for this treatment[10,11].

The treatment was administrated in the back and lower limbs for 20 min. every night about an hour before bed. The aroma that used were; aromatic plant oils (Melissa-based, lavender and lemon balm oil).

Physical Activity
Physical activity has been shown very promising results on the reduction of many BPSD and it seems that it could be an effective non-pharmacological intervention for sleeping problems, as well[12,13]. Our intervention was administrated every day for 30 min. All the family caregivers chose walking, as the easiest physical activity for their patients.

2.4 Measures

Mini Mental State Examination (MMSE)[14,15]: MMSE is a 30-point questionnaire that is used to evaluate the cognitive impairment.

Addenbrooke's Cognitive Examination Revised (ACE-R)[16,17]: ACE-R is a 100-point questionnaire that includes MMSE. It is highly sensitive and can be used for the diagnosis of dementia.

Geriatric Scale of Depression (GDS)[18,19] : This scale it is a questionnaire of 30 questions (YES/ NO) that examines if the patient has depressive symptoms.

Functional Rating Scale for Symptoms in Dementia (FRSSD)[20]: It is a scale to access the daily functioning ability and includes 14 different daily activities.

Neuropsychiatric Inventory (NPI)[21,22] : The questionnaire is administrated to the caregiver. It evaluates the frequency and severity of the symptom as long as the impact that each behaviour has on the caregiver.

2.5 Data Analysis

Categorical variables were presented as percentages while continuous variables were presented as Mean value and Standard Deviation (SD). The Shapiro-Wilk test for normality was used to assess the normality assumption for continuous variables. Correlations between continuous variables were quantified with the Spearman's rho correlation coefficient. Comparisons of means were conducted using the independent samples t-test. The General Linear Model (GLM) was used to model the effect of the independent factors and covariates on the continuous variables of interest. Fisher'sleast significant difference(LSD) was used for the post-hoc comparisons. P values less than 0.05 were considered statistically significant. SPSS 24.0 (IBM Inc., Armonk, NY) was used for the statistical analysis.

3. RESULTS

56,6% diagnosed with AD, 5% with LB, PDD and Mixed dementia, 10% with FTLD, 13,3% MCI patients, 3,3% with VaD and 1,6% with Aids. Study participants had a mean age of 74.3 years (SD 8.6). Twenty nine of them were females (48,3%). The mean years of education were 9.9 (SD 4.5). The mean MMSE score was 19.7 (SD 5.5), for GDS was 8.1 (SD 5.2), for ACE was 56.3 (19.3) and for FRSSD was 15.8 (SD 10.4). According to NPI there are two results as well; a) result of which of the three treatments reduced the problem and b) result of which treatment had a greater impact on caregiver's distress.

Table 1 shows the demographic characteristics of the 60 patients of the sample. There was no significant difference between males and females in MMSE (p=0.292), GDS (p=0.648), ACE (p=0.458) and FRSSD (p=0.406). Moreover, there was no significant correlation between age and MMSE (p=0.192), GDS (p=0.236), ACE (p=0.112) and FRSSD (p=0.502), as well as between years of education and MMSE (p=0.295), GDS (p=0.311), ACE (p=0.129) and FRSSD (p=0.564).

General Linear Model (GLM) results showed that treatment had a significant effect on "structured bedtime routine" regardless the group and the time of applying the non-pharmacological interventions. Specifically, NPI after "structured bedtime routine" (mean (SD) = 5.97 (1.74)) was significantly lower than "aromatherapy and massage therapy" (7.58 (2.26), p<0.001) and "physical activity" (7.02 (2.04), (p=0.06).

The same treatment had a significant result on Distress (p<0.001). Distress was significantly lower after "structured bedtime routine" (2.22 (0.67)) as compared to Distress after "aromatherapy and massage therapy" (3.12 (0.96), p<0.001) and after "physical activity" (2.85 (0.89), p<0.001).

Table 2 gives Means and SDs of the Descriptive Statistics of the NPI after each treatment and caregiver's Distress. The mean Distress for treatment "structured bedtime routine" is 2.22 (SD 0.67), for "aromatherapy and massage therapy" is 3.12 (SD 0,96) and for "physical activity" is 2.85 (SD 0.89).

There was no difference on NPI between the different groups (p=0.093) on the time that the treatment was prescribed (p=0.683). Similarly, there was no difference on Distress between the different groups (p=0.482) on the time that the treatment was prescribed (p=0.691).

4. DISCUSSION

This study showed that "psychoeducational programme of the caregivers- structured bedtime routine" seems to be the more efficient intervention. The second more efficient intervention is "physical activity" and the third "aromatherapy and massage therapy".

Structured bedtime routine has not been well reviewed until now in the literature[23,24]. There is a lack of clinical trials using this non-pharmacological intervention in order to reduce insomnia, getting up in the middle of the night and / or early awaken in the morning. Sleep disturbances are sometimes one of the most important factors that leads to institutionalization[25]. However, according to the results, structured bedtime routine can reduce the sleeping problems and the distress of the caregiver. One possible explanation could be that caregivers can also have a balanced programme and they do not waken up in the middle of the night to take care of their patients. According to the results, the caregivers show less distress while using this intervention.

Furthermore, walking is the easiest way to exercise and it was preferable from all the participants. Thirty (30) min. of walking everyday showed that it can reduce the sleeping disturbances and the distress of the caregiver. Increase physical activity has been shown in previous studies that has positive results. Specifically, one study used a mixed-method approach in order to evaluate some non-pharmacological interventions for sleeping disorders. This study used bright light therapy, exercise and sleep hygiene education. Although, the trial completed by only nine participants and there was no control group, however the results for physical activity were promising[26]. Moreover, one review mentioned that there is a strong need of further research, because the type, frequency and duration of the exercise remain unclear. Most

studies suggest walking for at least 30' for several times in a week[27]. Another exploratory study mentioned improvements in night-sleep, though it used a small sample size (9 pairs)[28]. Vigorous activity indicated improvements in sleeping disorders, if the exercise takes place for 1 hour, 3 times a week for 6 months. Furthermore, another review underlined that daily walking for 30' for 5 days a week can show improvements on sleeping disturbances[29]. A large systematic review declared also positive results in increasing the duration of sleep and decrease the night-time awakenings, but on the other hand claims that the studies so far have used small sample size and they lack of rigorous methods[30]. A randomized trial in 1999 and other two in 2005 have shown positive results in increasing night-time sleep and decreasing daytime sleep and night awakenings. In particular the first study in 1999 used physical activity for 14 weeks plus a night-time programme that lasted for 5 nights in order to decrease noise. The trial used an intervention and control group[31]. The same authors in 2005 also found positive results of exercise on sleeping problems. Their intervention took place for 30' or more with daily sunlight exposure and had promising results on reducing the day sleeping[32]. Finally, the last trial used daily walking in the sun and found positive results in decreasing night insomnia[33].

However, according to some other studies physical activity does not have a significant impact on sleeping problems in dementia. It seems that the duration and the type of exercise that has the most beneficial effects still remain unclear[3435] . Therefore, there is a need of further research[36 37] .

"Aromatherapy and massage therapy" is a combination of oils and massage therapy had positive results according to the literature so far[38 39] . Although, there is a lack of strong evidence that aromatherapy and massage therapy can solve the sleeping problems in PwD, there are a few trials that have shown promising results[40]. A pilot single-blinded cross-over study aimed to evaluate the efficacy of lavandula augustifolia (lavender). The trial showed promising results although it underlined the importance of a large study[41]. Another study used lavender and rosemary in a large trial with 144 participants who were randomly assigned to three groups. The results were promising for sleeping problems[42]. However, a Cochrane review underlines the importance of further research for both aromatherapy and massage therapy[43].

This study has limitations including that the caregivers provided all the interventions by themselves. Another limitation is that BLT therapy that has been shown as effective could not be used in the current study. Moreover, the interventions lasted for one week and therefore may had some beneficial effects if they lasted longer. Serious attention should be also provided on how much the interventions should last. A follow-up should be required. Furthermore, the psychoeducational intervention has the extra benefit that a professional clinician guided the caregiver and therefore this might have affected the results.

Future studies should use larger sample sizes, solid statistical analysis and a follow-up session in order to examine if the beneficial effects of the interventions last and how much time. Studies which will clarify the effect of physical exercise should identify which type of exercise seem to be the most efficient and which is the right duration.

It seems that there is a strong need of further research.

5. CONCLUSION

In this study the more effective non-pharmacological intervention for the sleeping disturbances in PwD was "psychoeducational programme for the caregivers- structured bedtime routine". Non-pharmacological interventions is the alternative that future studies should focus on.

CONFLICT OF INTEREST

The authors have no conflict of interest to report

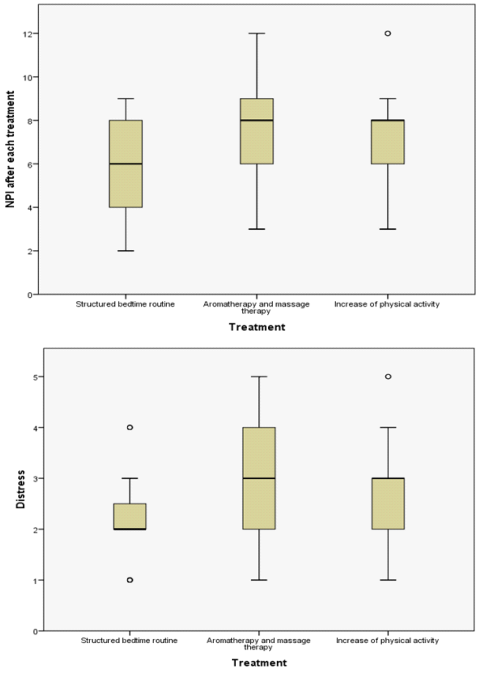
Table 1: Demographic Characteristics of the total sample-Means and Standard Deviation

	Males (N=31)	Females (N=29)	Both (N=60)
A Age, Mean (SD	79.29 (9.83)	76.52 (6.46)	74.33 (8.7)
Y Years of Education, Mean(SD)	11.03 (4.42)	8.72 (4.40)	9.92 (4.53)
MMSE, Mean (SD)	20.45 (5.18)	18.93 (5.90)	19.72 (5.55)
GDS, Mean (SD)	8.42 (5.78)	7.79 (4.69)	8.12 (5.24)
ACE, Mean (SD)	58.16 (20.08)	54.41 (18.70)	56.35 (19.35)
FRSSD, Mean (SD)	14.68 (10.49)	16.93 (10.35)	15. 77 (10.40)

Table 2 Descriptive Statistics between the different treatments prescribed for NPI and Distress.

	NPI	Distress
Treatment	Mean (SD)	Mean (SD)
structured bedtime routine	5.97 (1.74)b	2.22 (0.67)b
aromatherapy and massage therapy	7.58 (2.26)a	3.12 (0.96)a
increase physical activity	7.02 (2.04)a	2.71 (0.92)a

Superscripts a, b: flag significant differences for each column.



REFERENCES

1. Lolk A, Andersen K. Behavioural disturbances in dement patients. Ugeskr Laeger, 2017; 179(12); pii: V10160740.
2. Torrisi M, De Cola MC, Marra A, De Luca R, Bramanti P, Calabro RS. Neuropsychiatric symptoms in dementia may predict caregiver burden: a Sicilian exploratory study. Psychogeriatrics, 2017; 17(2): 103-107.
3. Mattis J. Circadian Rhythms, Sleep, and Disorders of Aging. Trends Endocrinol Metab., 2016; 27(4): 192-203.
4. Reynold CF, Butters MA, Lopez O, Pollock BG, Dew MA, Mulsant BH, et al. Maintenance Treatment of Depression in Old Age: A Randomized, Double-blind, Placebo-Controlled Evaluation of the Efficacy and Safety of Donepezil Combined with Antidepressant Pharmacotherapy. Atch Gen Psychiatry, 2011; 68(1): 51-60.
5. Brown CA, Wielandt P, Wilson D, Jones A, Crick K. Healthcare Providers' Knowledge of Disordered Sleep, Sleep Assessment Tools, and Nonpharmacological Sleep Interventions for Persons Living with Dementia: A National Survey. Sleep Disord., 2014; 2014: 286274.
6. Alessi CA, Martin JL, Webber AP, Cynthia E, Harker JO, Josephson KR. Randomized, controlled trial of a nonpharmacological intervention to improve abnormal sleep/wake patterns in nursing home residents. J Am Geriatr Soc., 2005; 53(5): 803-810.
7. Beinart N, Weinman J, Wade D, Brady R. Caregiver Burden and Psychoeducational Interventions in Alzheimer's Disease: A Review. Dement Geriatr Cogn Disord Extra 2012; 2:638–648.
8. Tremont G, Davis JD, Ott BR, Galioto R, Crook C, Papadonatos GD, et al. Randomized Trial of the Family Intervention: Telephone Tracking—Caregiver for Dementia Caregivers: Use of Community and Healthcare Resources. J Am Geriatr Soc., 2017; 65(5): 924-930.
9. Takeda A, Watanuki E, Koyama S. Effects of Inhalation Aromatherapy on Symptoms of Sleep Disturbance in the Elderly with Dementia. Evid Based Complement Alternat Med., 2017; 2017: 1902807.
10. Fung JK, Tsang HW, Chung RC. A systematic review of the use of aromatherapy in treatment of behavioral problems in dementia. Geriatr Gerontol Int., 2012; 12(3): 372-382.
11. Jimbo D, Kimura Y, Taniguchi M, Inoue M, Urakami K. Effect of aromatherapy on patients with Alzheimer's disease. Psychogeriatrics, 2009; 173-179.
12. _299 173..179
13. Lowery A, Cerga-Pashoja S, Lliffe S. The effect of exercise on behavioural and psychological symptoms of dementia: the EVIDEM-E randomised controlled clinical trial. Int J Geriatr Psychiatry, 2014; 29(8): 819-827.
14. Legere LE, McNeill S, Martin LS, Acorn M, An D. Non-pharmacological approaches for behavioural and psychological symptoms of dementia in older adults: A systematic review of reviews. J Clin Nurs., 2017; doi: 10.1111/jocn.14007 [Epub ahead of print].
15. Folstein MF, Robins LN, Helzer JE. The mini-mental state examination. Arch Gen Psychiatry, 1983; 812-822.
16. Fountoulakis KN, Tsolaki M, Chantzi H, Kazis A. Mini Mental State Examination (MMSE): A

validation study in Greece. Am J Alz Dis Other Demen., 2000; 15(6): 342-345.
17. Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. Neurology, 2000; 55(11): 1613-1620.
18. Konstantinopoulou E, Kosmidis MH, Ioannidis P, Kiosseoglou G, Karacostas D, Taskos N. Adaptation of Addenbrooke's Cognitive Examination-Revised for the Greek population. Eur J Neurol., 2011; 18(3): 442-447.
19. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: A preliminary report. J Psych Res., 1983; 17: 37-49.
20. Fountoulakis KN, Tsolaki M, Iakovides A, Yesavage J, O'Hara R, Kazis A, et al. The validation of the short form of the Geriatric Depression Scale (GDS) in Greece. Aging (Milano), 1999; 11(6): 367-372.
21. Hutton JT, Dippel RL, Loewenson RB. Functional rating scale for the symptoms of dementia. In J. J. Gallo, W, Reichel and L, Andersen (Eds.) Handbook of geriatric assessment. Rockville, MD: Aspen Publishers, 1998: 77-80.
22. 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: 2308-2314.
23. Politis AM, Mayer LS, Passa M, Mailis A, Lyketsos C. Validity and reliability of the newly translated Hellenic Neuropsychiatric Inventory (H-NPI) applied to Greek outpatients with Alzheimer's disease: a study of disturbing behaviors among referrals to a memory clinic. Geriatr Psychiatry, 2004; 19(3): 203-208.
24. Salami O, Lyketsos C, Rao V. Treatment of Sleep Disturbance in Alzheimer's Dementia. Int J Geriatr Psychiatry, 2011; 26(8): 771–782.
25. Forlenza OV, Loureiro JC, Pais MV, Stella F. Recent advances in the management of
26. neuropsychiatric symptoms in dementia. Curr Opin Psychiatry, 2017; 30(2): 151-158.
27. Dimitriou TD, Tsolaki M. Evaluation of the efficacy of randomized controlled trials of sensory stimulation interventions for sleeping disturbances in patients with dementia: a systematic review. Clin Interv Aging, 2017; 12: 543-548.
28. Gibson RH, Gander PH, Dowell AC, Jones LM. Non-pharmacological interventions for managing dementia-related sleep problems within community dwelling pairs: A mixed-method approach. Dementia, 2016; doi: 10.1177/1471301215625821
29. Thune-Boyle IC, Iliffe S, Cerga-Pashoga A, Lowery D, Warner J. The effect of exercise on behavioral and psychological symptoms of dementia: towards a research agenda. Int Psychogeriatr., 2012; 24(7): 1046-1057.
30. Nascimento CM, Ayan C, Cancela JM, Gobbi LT, Gobbi S, Stella F. Effect of a multimodal exercise program on sleep disturbances and instrumental activities of daily living performance on Parkinson's and Alzheimer's disease patients. Geriatr Gerontol Int., 2014; 14(2): 259-166.
31. Ooms S, Ju YE. Treatment of Sleep Disorders in Dementia. Curr Treat Options Neurol., 2016; 18: 40.
32. O'Neil ME, Freeman M, Christensen V, et al. A Systematic Evidence Review of Non-pharmacological Interventions for Behavioral Symptoms of Dementia [Internet]. Washington (DC): Department of Veterans Affairs (US); 2011 Mar. Available from: https://www.ncbi.nlm.nih.gov/books/NBK54971/
33. Alessi CA, Yoon EJ, Schelle JF, Samarrai ANR, Cruise PA. A randomized trial of a combined physical activity and environmental intervention in nursing home residents: do sleep and agitation improve? J Am Geriatr Soc., 1999; 47: 784-791.
34. Alessi CA, Martin JL, Webber AP, Cynthia KE, Harker JO, Josephson KR. Randomized, controlled trial of a nonpharmacological intervention to improve abnormal sleep/wake patterns in nursing home residents. J am Geriatr Soc., 2005; 53(5): 803-810.
35. McCurry SM, Gibbons LE, Logsdon RG, Vitiello MV, Teri L. Nighttime insomnia treatment and education for Alzheimer's disease: a randomized, controlled trial. J Am Geriatr Soc., 2005; 53: 793-802.
36. Abraha I, Rimland JM, Trotta FM, Dell'Aquilla G, Cruz-Jentoft A, Petrovic M, et al. Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR- On Top series. BMJ Open, 2017; e012759.
37. Eggermont LH, Scherder EJ. Physical activity and behaviour in dementia: a review of the literature and implications for psychosocial intervention in primary care. Dementia, 2006; 5: 411-428.
38. McCurry SM, Reynolds CF, Ancoli-Israel E, Teri L,Vitiello MV. Treatment of sleep disturbance in Alzheimer's disease. Sleep Med Rev., 2000; 4: 603-628.
39. Deschenes CL, McCurry SM. Current treatments for sleep disturbances in individuals with dementia. Curr Psych Reports, 2009; 11: 20-26.
40. Scuteri D, Morrone LA, Rombola L, Avato PR, Bilia AR, Corasaniti MT, et al. Aromatherapy and Aromatic Plants for the Treatment of Behavioural and Psychological Symptoms of Dementia in Patients with Alzheimer's Disease: Clinical Evidence and Possible Mechanisms. Evid Based Complement Alternat Med., 2017; 9416305. doi: 10.1155/2017/9416305.
41. Takeda A, Watanuki E, Koyama S. Effects of Inhalation Aromatherapy on Symptoms of Sleep Disturbance in the Elderly with Dementia. Evid Based Complement Alternat Med., 2017; 2017:1902807. doi: 10.1155/2017/1902807.
42. Nguyen QA, Paton C. The use of aromatherapy to treat behavioural problems in dementia. Int J Geriatr Psychiatry, 2008; 23: 337-346.
43. Lewith GT, Godfrey AD, Prescott P. A single-blinded, randomized pilot study evaluating the aroma of Lavandula augustifolia as a treatment for mild insomnia. J Altern Complement Med., 2005; 11(4): 631-637.
44. Moss M, Cook J,Wesnes K, Duckett P. Aromas of rosemary and lavender essential oils differentially affect cognition and mood in healthy adults. Int J Neurosci 2003; 113: 15–38.
45. Thorgrimsen L, Spector A, Wiles A, Orrell M. Aroma therapy for dementia. Cochrane Database Syst Rev., 2003; (3): CD003150.