ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 01 | January - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

NON-PHARMACOLOGICAL INTERVENTIONS FOR DEPRESSIVE SYMPTOMS IN DEMENTIA. A CROSS-OVER RCT.

Neurology

Dimitriou Tatiana-Danai*	PhD, 1st Department of Neurology, Aristotle University of Thessaloniki, Greece. *Corresponding Author
Papatriantafyllou John	Psychiatrist, PhD, MD 3rd Age Center IASIS, 2nd Neurology Dpt., University of Athens, 'Attikon' Hospital.
Konsta Anastasia	MD, PhD, Ass. Professor, 1st Department of Psychiatry, "Papageorgiou" General Hospital of Thessaloniki, Aristotle University of Thessaloniki, Greece.
Kazis Dimitrios	MD, PhD, Ass. Prof. 3rd Neurology Department Aristotle University of Thessaloníki.
Athanasiadis Loukas	MD, PhD, Ass. Professor, 1st Department of Psychiatry, "Papageorgiou" General Hospital of Thessaloniki, Aristotle University of Thessaloniki, Greece.
Ioannidis Panagiotis	MD, PhD, Ass. Professor, 2nd Department of Neurology, Aristotle University of Thessaloniki, Makedonia, Greece.
Koutsouraki Efrosini	MD, PhD, Ass. Professor, 1st Department of Neurology, Aristotle University of Thessaloniki, Makedonia, Greece.
Tegos Thomas	MD, PhD, Ass Professor, 1st Department of Neurology, Aristotle University of Thessaloniki, Makedonia, Greece.
Tsolaki Magdalini	MD, PhD, Neuropsychiatrist, Professor, Director of the 1st Department of Neurology, Aristotle University of Thessaloniki, Makedonia, Greece.

ABSTRACT

Background: Depression is accompanied by the early stages of Alzheimer's disease (AD) and other forms of dementia. Depression can influence the daily functioning of the patients with dementia (PwD) and their cognitive abilities. Sometimes it is hard to diagnose because it may seem like apathy. The current pharmacological treatment can manage depressive symptoms, however the side effects of the drugs are severe. **Methods:** Sixty (60) PwD randomly assigned in six (6) different groups of 10 participants each. They received three non-pharmacological interventions: a) Reminiscence Therapy (RT), b) Body Exercise (BE) and c) Music Therapy (MT). The study is a cross-over randomized controlled trial including patients with different types of dementia and at different stages of dementia. The neuropsychological examination before the interventions included: MMSE, ACE-R, GDS, FRSSD and NPI Questionnaire (sub-questions only for depression). The interventions lasted for 5 days and there were 2 days off as a washout period. There was no drop-out rate. **Results:** The combination of MT (p=0.012)- BE (p=0.020)- RT (p=0.041) is the sequence of the interventions that can reduce depression. For the caregivers, we had the same combination with the best results as well: MT (p=0.002)- BE (p=0.006)- RT (p=0.012). **Conclusions:** There is a combination of non-pharmacological interventions that can reduce statistically significant the depression in patients with dementia (PwD) and their caregivers.

KEYWORDS

Randomized Controlled Trial, BPSD, Dementia, Non-pharmacological interventions, depression

1. INTRODUCTION

Depression is accompanied the early stages of Alzheimer's disease (AD) and other forms of dementia, but there is no clear association yet, between the severity of AD or dementia and the frequency of depression.[1] It seems that almost 50% of the patients with dementia (PwD) may experience depressive symptoms, however the statistics should be not taken for granted, because the rate varies in terms of the methods and sample.[2] Nevertheless, the rate of depression during the different stages of dementia is more common than in the healthy elderly population. Sometimes depression is the first symptom of AD, Vascular Dementia (VaD) and Parkinson Dementia (PDD)[3]. Depression can be a predictor or a risk factor of AD. However, at the same time it is also known that accumulation of β-amyloid can be detected many years before AD.[4] Therefore, the onset of depression may reflect a progressive neuropathological process leading to AD.

Clinicians may under-diagnose depression over dementia. Frequently, depression co-exists with apathy and many times clinicians misdiagnose depression over apathy and vice versa.[5] The typical symptoms of depression include feelings of guilt, lack of interest (anhedonia), depressed mood, feeling worthlessness, and suicidal ideation.[6] In the case of an elderly patient, it is critical to evaluate the depressive symptoms and examine further if dementia co-exists. Depression can influence the daily functioning of PwD and their cognitive abilities.[7] The progress and severity of dementia can be influenced by depression. Several macroscopic brain alterations have been suggested to occur over depressive symptoms. The pathophysiology of depression has shown implications in the hippocampus, anterior cingulate cortex, dorsolateral prefrontal cortex, insula, and superior temporal gyrus [(6)]. In particular, the reduced activity of the dorsolateral prefrontal cortex is associated with cognitive declines, because this area is involved in working memory and planning [(6)].

Depression has a good therapeutic response to antidepressants drugs in PwD, but the cognitive decline will remain and progress.[8] It seems that there are many pharmacological treatment options available, but their efficacy still remains uncertain. Their side effects in aging populations should be taken into serious consideration. Acetylcholinesterase inhibitors and memantine need further evidence in order to come to safe conclusions, if they can effectively treat depression. On the other hand, antipsychotics and mood stabilizers have no positive effects for depression and have many severe side-effects [(9)]. It is critical to mention that pain may play a major role, because PwD may experience pain and so this may have significant effects on their mood. Hence, it is crucial to find other solutions such as non-pharmacological interventions.

The current study evaluated three different non-pharmacological interventions in order to find the most effective combination for the reduction of the depressive symptoms in PwD and their caregivers. The interventions are: a) Body Exercise (BE), b) Reminiscence Therapy (RT) and c) Music Therapy (MT).

2. MATERIALS AND METHODS

2.1 Participants

There were sixty (60) PwD in the current study. The PwD visited 2 University Departments of General Hospitals of Thessaloniki and one in Athens. The caregivers have been informed and given written consent. The PwD were diagnosed by neurologists-psychiatrists of the General Hospitals. We received an approval from the Ethics Committee of Alzheimer Hellas (12-06/90/2012) We included patients with Alzheimer's disease (AD), Vascular dementia (VAD), Lewy Body Dementia (LBD), Parkinson's Dementia (PDD), Frontotemporal Lobal Degeneration (FTLD), Mixed dementia (AD & VAD), AIDS and patients in Mild Cognitive Impairment (MCI) level. All participants suffered from depressive symptoms according to NPI (questions and sub-questions for depression).

Table 1 shows the baseline characteristics of the sample. Twenty-three (23) patients were males (38.3%). The average age of the sample was 74.7 years old (SD 6.76) and the level of education was 9.52 (SD 4.47) years.

2.2 Procedure

All the measurements were applied at the baseline before any intervention and the scores were recorded. The participants were randomly assigned in 6 different groups of 10 patients each. Every group received the same interventions (above-mentioned) but in a cross-over designed. This means that the sequence of the procedure was different among groups (table 2). Each treatment was taken place for five days and at the morning of the 6th day, the results of NPI questionnaire (Depression questions and sub-questions of NPI) were recorded. There was two -day break as a wash-out period. There was no drop-out rate.

2.3 Interventions

The non-pharmacological interventions were chosen because of the following four (4) factors: a) they could be easily performed by the caregivers (spouses and children) who were informal caregivers, b) they were pleasurable and had no side-effects, c) they belong to different non-pharmacological categories: RT is a cognitive intervention, MT is a sensory intervention and BE belongs to “other interventions”. Lastly, d) they have been used in previous studies with significant results.

A) Exercise / Physical Activity (BE)

Regarding the duration of the BE, the review claims that most studies were unable to specify a duration time[10,11,] whereas others provided details of the frequency and duration: studies have reported that 30-45' min. of BE, for three times a week may have positive results[12 13]. A higher frequency of BE is related to better results. In the current study we used walking, as the easiest physical activity. The intervention applied for 30' min. once a day, for five days, every morning after breakfast.

B) Reminiscence therapy (RT)

Reminiscence therapy is used in order to recall past memorable events of the patient's life. Photos, music, books, and letters have been used. A large Cochrane review[14] refers to previous studies and the length of RT interventions that they have used; it seems that the duration of RT ranged from 60-90min. The current study applied RT for 60min. every day for five days every morning after breakfast.

C) Music therapy (MT)

Music Therapy (MT) has shown promising results in reducing depression symptoms. However, it is not still known what type of music and which duration of this intervention is needed. Many studies have mentioned beneficial effects [15 16]. In the current study, the caregivers chose the preferable music for their patients. A recent study showed that listening to music for 30-50' minutes per day, in the course of a week, can have a beneficial effect[17]. In this study MT demonstrated for 45min. once per day, for five days a week, every morning after breakfast.

2.4 Measures

Mini Mental State Examination (MMSE)[18 19] : MMSE is a 30-point questionnaire that is used to evaluate the cognitive status. It is used to estimate the severity of cognitive decline. The questionnaire examines registration, attention, recall, language, and orientation. Higher scores indicate better cognitive performance and lower scores severe cognitive decline.

Addenbrooke's Cognitive Examination Revised (ACE-R)[2021]: ACE is a 100-point questionnaire that is used to evaluate the cognitive impairment. It includes MMSE. It is highly sensitive and can be used as a screening test for dementia. It includes questions about orientation, registration, attention, concentration, recall, verbal fluency, memory, language, spatial abilities, perceptual abilities, and recognition. Higher scores indicate better cognitive performance.

Geriatric Scale of Depression (GDS)[2223] : This scale is a questionnaire of 30 questions that examines if the patient has depression. The patient answers with a YES / NO. Higher scores indicate higher level of depression. The current study used the GDS scale with the 30 questions.

Functional Rating Scale for Symptoms in Dementia (FRSSD)[2425] : It is a scale to access the Activities of Daily Living. The scale is a questionnaire for the caregiver and includes 14 different daily activities, such as; eating, dressing, incontinence, speaking, sleeping, faces' recognition, personal hygiene, name memory, fact memory, alertness, agitation, space orientation, emotional status, socializing. The scale is scored from 0-3 (whereas 0= fully independence and 3= fully dependence).

Neuropsychiatric Inventory (NPI)[26 27]**:** The questionnaire is administrated to the caregiver. It evaluates the frequency and severity of the symptom and the impact of the behavior to the caregiver. Frequency is scored from 0-4 (0= rarely happens, 4= happens every day), severity from 1-3 (1=mild severity, 3=severe) and the distress is scored from 0-5 (0= not at all, 5= extremely). The domain total score is the product of a) frequency X severity score and b) the total score of caregiver's distress. In the current study was used only the NPI questions referred to depression. The questions of NPI for depression are;

- Does the resident cry at times?
- Does the resident say or act like he/she is depressed?
- Does the resident put him/ herself down or say that he/she feels like a failure?
- Does the resident say that he/she is a bad person or deserves to be punished?
- Does the resident seem very discouraged or say that he/she has no future?
- Does the resident say he/she is a burden to the family or that the family would be better off without him/her?
- Does the resident talk about wanting to die or about killing himself/ herself?
- Does the resident show any other signs of depression or sadness?

2.5 Data Analysis

Categorical variables were presented as percentages while continuous variables were presented as Mean value and Standard Deviation (SD). Wilcoxon signed-rank test used, because the distribution of the differences between the samples cannot be assumed to be normally distributed. Chi-square test was used in order to find differences in gender in the 6 groups and finally z value score was used in order to find the type of dementia in each group. P values less than 0.05 were considered statistically significant. SPSS 25.0 (IBM Inc., Armonk, NY) was used for the statistical analysis.

3. RESULTS

The sample of the study was sixty (60) PwD of whom 56% suffered from AD, 1.6% from VaD, 21.4% from MCI, 4.9% from LBD, 4.9% from PDD and 9.9% from FTD (table 3).

There were no differences between males and females between the six categories defined by the sequence schemes (p=0.474). Furthermore, no differences were found on age (p=0.875), years of education (p=0.932), MMSE (p=0.749), ACE-R (p=0.575), GDS (p=0.197), NPI Result (p=0.539) and NPI Distress (p=0.517) at baseline assessment in 6 different groups. There was no relationship between the categories and the disease diagnosis (p=0.082). Chi-square was used for the evaluation of the differences in gender. Pearson chi-square score was p=0.314 for gender, which means there is no statistically significant difference among groups. Z scores were used for diagnosis: group 1 had a mean score of 4.50 (SD 4.11) in depression scale of NPI, group 2 had 3.57 (SD 4.39), group 3 had 4.40 (SD 3.50), group 4 had 2.10 (SD 2.84), group 5 had 4.70 (SD 3.86) and group 6 had 3 (SD 3.74) at baseline.

According to Wilcoxon test the group that had the most effective combination that reduced depression statistically significant was group 5. Group 5 included 4 males and 6 females. In this group 30% of the sample had AD, 10% VaD, 30% PDD and 30% MCI. For group 5 the baseline NPI was 8.5± 2.54. When the interventions applied in the following sequence, statistically significant results were found: MT (p=0.012), followed by BE (p=0.002), followed by RT (p=0.041). The same combination was also the most effective for the reduction of caregivers' distress because of depression in their PwD. For group 5 the baseline NPI was 4± 0.82. When the interventions applied in the following sequence, caregivers' burden was reduced: MT (p=0.002), followed by BE (p=0.006), followed by RT (p=0.012). The results of all groups are shown on table 4.

4. DISCUSSION

Our study evaluated three non-pharmacological interventions for the management of depression in PwD. According to our results MT seems to have beneficial effects. Our results are in accordance with the current literature. Most studies have used a small sample size; an RCT with 15 participants (N=15) for a total of 16 weeks applied once a week MT intervention for 20min. The trial mentions positive results of MT in treating depressive symptoms[28]. Moreover, another RCT of 17 (N= 17) patients and a total of 8-10 sessions once a week for less than 60min. also reported positive results[29]. The two trials in 2008[30] and 2010[31] by the same author also mentioned beneficial effects. The trial in 2008 had 30 patients (N=30) in experimental group and 29 (N=29) patients in control group. The experimental group received 16 weeks of MT whereas the control group received educational support or other activities. The trial in 2010 had also 30 participants (N=30) in experimental group and 30 (N=30) in control group and received three cycles of 12 MT sessions each, three times per week for 30min. each session. Every cycle was followed by one-month wash-out and the trial reported positive effects. Another RCT with 8 patients (N=8) lasted for 3 months (25 sessions), applied twice a week the intervention for 60min. and reported positive effects.[32]

According to a trustful review (AMSTAR= 6) there are 4 RCT that have studied BE and depression[33]. The first trial had a sample of 43 patients (N=43) and applied Tai Chi for 60min. 3 times per week for 40 weeks. The trial did not find any significant positive results.[34] Moreover, another trial with 134 participants (N=134), applied walking for 60min. twice per week for 40 weeks and in the follow-up after 12 months mentioned no statistically significant improvements.[35] Additionally, another trial with 25 PwD (N=25) combined BE with MT for 30min. daily for 12 weeks and the follow-up assessment after 3 months found no statistically significant improvements, as well.[36] Another RCT with 14 PwD of AD (N=14) applied aerobic, balance, strength and walking repeated at 6 and 12 weeks and lasted for 2 hours each time but found no significant improvements[37]. In addition, another RCT used walking five days per week for 16 weeks. The trial categorized the participants into three experimental groups; a) comprehensive individual exercise, b) supervised individual exercise and c) attention control group. The sample was consisted of 96 participants with AD (N=96). This study mentions clear benefits from exercise.[38] There is a strong need for further research on the current matter. There are reviews which did not come to conclusions, because they used stringent inclusion criteria and they were unable to come to reliable evidence [39,40]. Moreover, one large review [10] mentions positive results on exercise but their outcomes rely on clinical experience than on scientific evidence.

RT intervention if applied as a third intervention, after MT and BE, can reduce further the depression. The studies, so far, seem to lack of methodological quality (AMSTAR=1)[41,42,43] . A recent large Cochrane review[44] identified 10 RCT but reported no significant differences. The review claims that RT has little or no improvement.

It is obvious from the above discussion that there is no study until today which used a combination of non- pharmacological interventions. One important conclusion of our study is that there is an effective combination of non-pharmacological interventions that can reduce depression symptoms in PwD and their caregivers. The combination is: MT- BE- RT. It is important to mention that the same combination that reduced depression in PwD, reduced caregivers' burden, as well. This can be logically explained; caregivers' psychology depends on the patient's behavior. Therefore, if the frequency or the intensity of the depression symptoms can be controlled, the caregivers' burden can be reduced too. Another important finding is that sensory stimulation intervention (MT) is more effective if applied first. Likewise, cognitive stimulation intervention (RT) is more effective when applied third, after a sensory stimulation intervention and BE.

The strength of the current study is that we used a quite large sample size (N=60). The methodological quality prevents some risk bias. The sequence of the interventions does not interfere with the results. In addition, apart from the heterogeneity of the sample, it seems that our results affect both genders, different types and stages of dementia. NPI questionnaire is a valid, reliable, and flexible scale to use. It can evaluate a wide range of psychopathology and it can be used across different ethnic group[45]. It is a matter of fact, that the caregivers spent more time with their patients, and this could be an explanation for our positive results. If this is the only explanation, we would wait that all the combinations we used could show beneficial effects. This underlines more the importance of our results. On the other hand, the limitations of the current study are the short duration of the interventions and the absence of follow-up. However, the caregivers needed direct solutions to their problems and therefore, the short length of the duration of the intervention may be justified. Future research should focus more on other combinations of non-pharmacological interventions, as the current pharmacological treatment may have side effects. It is crucial to establish the duration and type of MT that has the most positive results and identify the type, intensity, duration, and frequency of the BE, because it may be a promising alternative.

Role of authors

T. Dimitriou: author, researcher, statistical analyses
J. Papatriantafyllou: resources, supervision
A. Konsta: supervision
D. Kazsis: supervision
L. Athanasiadis: supervision
P. Ioannidis: supervision
T. Tegos: supervision
M. Tsolaki: designed the study, supervision, statistical analyses, edited the study

Conflict of interest

None.

Funding

None

ABBREVIATIONS

ACE-R: Addenbrooke's Cognitive Examination
AD: Alzheimer's Disease
LDB: Lewy Body Dementia
FTD: Frontotemporal Dementia
FRSSD: Functional Rating Scale for Symptoms in Dementia
GDS: Geriatric Depression Scale
MCI: Mild Cognitive Impairment
MMSE: Mini Mental State Examination
MT: Music Therapy
NPI: Neuropsychiatric inventory
PDD: Parkinson's Dementia
PwD: Patients with Dementia
RCT: Randomized Controlled Trial
RT: Reminiscence Therapy
VaD: Vascular Dementia

Table 1: Baseline characteristics of the sample

	Mean (SD) or N (%)
Males, N(%)	38.3%, (N=23)
Age	74.72 (6.76)
Years of education	9.52 (4.47)
MMSE	19.1 (5.19)
ACE-R	55.3 (18.1)
GDS	8.9 (4.68)
FRSSD	15.3 (9.9)
NPI Results	7.52 (2.28)
NPI Distress	3.43 (0.92)

Table 2: the sequence of the procedure: Intervention A: RT, Intervention B: Exercise, Intervention C: MT

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

Table 3: Percentages of the different types of dementia of the sample (N=60)

AD	VAD	LBD	PDD	FTD	MCI
56%	1.6%	4.9%	4.9%	9.9%	21.4%

Table 4: Wilcoxon for PwD

Group 1	Baseline NPI	NPI before intervention A	A-B	B-C
Mean score ± SD	8± 2.02	8± 2.02 - 6± 1.49	6± 1.49 - 6± 1.76	6± 1.76 - 6± 1.57
Percentiles		7.50-8.25, 6-8	6-8, 5.50-8	5.50-8, 4-6.50
p		0.034	0.741	0.339

group 2	Baseline NPI	NPI before	A-C	C-B
Mean score ± SD	8± 2.93	8± 2.93 - 6± 2.36	6± 2.36 - 4± 0.97	4± 0.97 - 6± 2.36
Percentile		4-9, 4-9	4-9, 4-6	4-6, 4-9
p		0.019	0.136	0.604

group 3	Baseline NPI	NPI before intervention B	B-A	A-C
Mean score ± SD	8± 2.17	8± 2.17 - 6± 2.18	6± 2.18 - 6± 1.83	6± 1.83 - 4± 1.08
Percentile		6-8.25, 4-8.25	4-8.25, 5.50-8.25	5.50-8.25, 4-6
p		0.016	0.559	0.011

group 4	Baseline NPI	NPI before intervention B	B-C	C-A
Mean score ± SD	8± 2.16	8± 2.16 - 7± 1.84	7± 1.84 – 3.5± 1.76	3.5± 1.76 - 7± 2.14
Percentile		5.25-8, 5.50-8	5.50-8, 3-6	3-6, 3.75-8
p		0.042	0.004	0.717

group 5	Baseline NPI	NPI before intervention C	C-A	A-B
Mean score ± SD	8.5± 2.54	8.5± 2.54 - 6± 1.83	6± 1.83 - 5± 1.63	5± 1.36- 4± 1.61
Percentile		6-9.75, 4-6	4-6, 3.50-6	3.50-6, 2-4
p		0.012	0.020	0.041

group 6	Baseline NPI	NPI before intervention C	C-B	B-A
Mean score ± SD	8± 2.58	8± 2.58 - 4± 1.49	4± 1.49 - 6± 1.49	6± 1.49, 6± 1.79
Percentile		6-8.25, 4-6	4-6, 6-8	6-8, 4-8
p		0.011	0.610	0.383

NPI Distress Wilcoxon

group 1	Baseline NPI	NPI before intervention A	A-B	B-C
Mean score ± SD	4± 1.07	4± 1.07 - 3± 0.87	3± 0.87 - 3± 0.91	3± 0.91- 2± 0.84
Percentile		2.75-4.25, 2-4	2-4, 2-4	2-4, 2-3
p		0.030	0.748	0.024

group 2	Baseline NPI	NPI before intervention A	A-C	C-B
Mean score ± SD	3± 1.15	3± 1.15 - 2± 2.78	2± 2.78 - 2± 0.57	2± 0.57 - 2± 1.11
Percentile		2-4, 2-3	2-3, 2-2	2-2, 1-3
p		0.033	0.102	0.589

group 3	Baseline NPI	NPI before intervention B	B-A	A-C
Mean score ± SD	3± 0.84	3± 0.84 – 2.5± 0.96	2.5± 0.96 - 3± 0.78	3± 0.78 - 2± 0.63
Percentile		3-4, 2-3.25	2-3.25, 2-3.25	2-3.25, 1-2
p		0.028	0.480	0.008

group 4	Baseline	NPI before intervention B	B-C	C-A
Mean score ± SD	3± 1.03	3± 1.03 – 2.5± 0.52	2.5± 0.52 – 2± 0.56	2± 0.56 - 3± 0.56
Percentile		2.75-3.50, 2-3	2-3, 2-2.25	2-2.25, 2.75-3
p		0.049	0.157	0.500

group 5	Baseline NPI	NPI before intervention C	C-A	A-B
Mean score ± SD	4± 0.82	4± 0.82 - 2± 0.82	2± 0.82 – 1.5± 0.67	1.5± 0.67- 1± 0.67
Percentile		3-4, 2-3	2-3, 2.25-3	2.25-3, 1-2
p		0.002	0.006	0.012

group 6	Baseline NPI	NPI before intervention C	C-B	B-A
Mean score ± SD	3.5± 0.84	3.5± 0.84 - 2± 0.47	2± 0.47 - 3± 0.78	3± 0.78, 3± 0.63
Percentile		3-4, 2-2	2-2, 2-3.25	2-3.25, 2-3
p		0.036	0.308	0.861

REFERENCES

1. Burke AD, Goldfarb D, Bollam P, Khokher S. Diagnosing and Treating Depression in Patients with Alzheimer's Disease. *Neurol Ther*. 2019;8(2):325-350.
2. Ryu SH, Jung HY, Lee KJ, Moon SK, Lee DW, Hong N, et al. Incidence and Course of Depression in Patients with Alzheimer's Disease. *Psychiatry Investig*., 2017; 14(3): 271-280.
3. Wiels W, Baeken C, Engelborghs S. Depressive Symptoms in the Elderly-An Early Symptom of Dementia? A Systematic Review. *Front Pharmacol*. 2020; 11:34.
4. Herbert J, Lucassen PJ. Depression as a risk factor for Alzheimer's disease: Genes, steroids, cytokines and neurogenesis - What do we need to know? *Front Neuroendocrinol*. 2016;41: 153-171. doi:10.1016/j.yfrne.2015.12.001
5. Burke AD, Goldfarb D, Bollam P. Diagnosing and treating depression in patients with Alzheimer's disease. Neurol Ther., 2019; 8: 325-350.
6. Galts CPC, Bettio LEB, Jewett DC, et al. Depression in neurodegenerative diseases: Common mechanisms and current treatment options. *Neurosci Biobehav Rev*., 2019; 102:56-84. doi:10.1016/j.neubiorev.2019.04.002
7. Terracciano A, Iacono D, O'Brien RJ, Troncoso JC, An Y, Sutin AR. Personality and resilience to Alzheimer's disease neuropathology: a prospective autopsy study. *Neurobiol Aging*, 2013; 34: 1045-1050.
8. Kratz T. The Diagnosis and Treatment of Behavioral Disorders in Dementia. *Dtsch Arztebl Int.*, 2017; 114(26): 447-454.
9. Ford AH, Almeida OP. Management of Depression in Patients with Dementia: Is Pharmacological Treatment Justified? *Drugs Aging*, 2017;34(2):89-95. doi:10.1007/s40266-016-0434-6
10. Thune-Boyle IC, Iliffe S, Cerga-Pashoja 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.
11. Abraha I, Rimland JM, Trotta FM, et al. Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series [published correction appears in BMJ Open. 2017 Jul 17;7(7):e012759corr1]. *BMJ Open*. 2017;7(3): e012759.
12. Edwards N, Gardiner M, Ritchie DM, Baldwin K. Sands L. Effect of exercise on negative affect in residents in special care units with moderate to severe dementia. *Alzh Dis Assoc Disord*., 2008; 22: 362-368.
13. Fleiner T, Leucht S, Forstl H, et al. Effects of Short-Term Exercise Interventions on Behavioral and Psychological Symptoms in Patients with Dementia: A Systematic Review. *J Alzheimers Dis.,* 2017; 55(4): 1583-1594.
14. Woods B, O'Philbin L, Farrell EM, Spector AE, Orrell M. Reminiscence therapy for dementia. Cochrane Data Syst Rev., 2018, 3. Art. No.: CD001120.
15 .de la Rubia Ortí JE, García-Pardo MP, Iranzo CC, et al. Does Music Therapy Improve Anxiety and Depression in Alzheimer's Patients? *J Altern Complement Med*. 2018;24(1):33-36.
16. Ueda T, Suzukamo Y, Sato M, Izumi SI. Effects of music therapy on behavioral and psychological symptoms of dementia: A systematic review and meta-analysis. *Ageing Res Rev*., 2013; 12: 628-641.
17. Craig J. Music Therapy to reduce agitation in dementia. *Nurs Times*, 2016; 110(32-33): 12-15.
18. Folstein MF, Robins LN, Helzer JE. The mini-mental state examination. *Arch Gen Psychiatry*, 1983; 812-822.
19. Fountoulakis KN, Tsolaki M, Chantzi H, et al. Mini Mental State Examination (MMSE): A validation study in Greece. *Am J Alz Dis Other Demen*., 2000; 15(6): 342-345.
20. Mathuranath PS, Nestor PJ, Berrios GE, et al. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology*, 2000; 55(11): 1613-1620.
21. 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.
22. 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.
23. Fountoulakis KN, Tsolaki M, Iacovides A, Yesavage J, O' Hara R, Kazis A, et al. The validation of the short form of the Geriatric Depression Scale (GDS) in Greece. *Ag Clin Exp Res.,* 1999; 11(6): 367-372.
24. 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 77-80, 1998.
25. Tsolaki M. Neuropsychological Evaluation of the Elderly. Melissa, Thessaloniki, 1997.
26. 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.
27. 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.
28. Guétin S, Portet F, Picot MC, et al. Effect of music therapy on anxiety and depression in patients with Alzheimer's type dementia: randomised, controlled study. *Dement Geriatr*

Cogn Disord., 2009; 28:36–46.
29. Miura H, Kanayama Y, Mogi N, et al. Effect and significance of music therapy on elderly persons with mild dementia. *Jap J Music Ther*., 2005; 5:48–57.
30. Raglio A, Belleli G, Traficante D, Gianotti M, Ubezio MC, Villani D, et al. Efficacy of music therapy in the treatment of behavioral and psychiatric symptoms of dementia. *Alzheimer Dis Assoc Disord.*, 2008; 22(2): 158-162.
31. Raglio A, Belleli G, Traficante D, Gianotti M, Ubezio MC, Gentile S, et al. Efficacy of music therapy treatment based on cycles of sessions: a randomized controlled trial. *Aging Ment Health,* 2010; 14(8): 900-904.
32. Suzuki M, Kanamori M, Nagasawa S, et al. Music therapy-induced changes in behavioral evaluations, and saliva chromogranin a and immunoglobulin a concentrations in elderly patients with senile dementia. Geriatr Gerontol Int., 2007; 7:61–71.
33. Potter R, Ellard D, Rees K, et al. A systematic review of the effects of physical activity on physical functioning, quality of life and depression in older people with dementia. *Int J Geriatr Psychiatry*, 2011; 26:1000–11.
34. Burgener SC, Yang Y, Gilbert R, et al. The effects of a multimodal intervention on outcomes of persons with early-stage dementia. *Am J Alzheimers Dis Other Demen*., 2008; 23:382–94.
35. Rolland Y, Pillard F, Klapouszczak A, et al. Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. *J Am Geriatr Soc.,* 2007;55: 158–65.
36. Van de Winckel A, Feys H, De Weerdt W, et al. Cognitive and behavioural effects of music-based exercises in patients with dementia. *Clin Rehabil*., 2004; 18:253–60.
37. Vital T, Hernandez S, Gobbi S, Costa J, Stella F. Systematized physical activity and depressive symptoms in Alzheimer's dementia: a systematic review. *J Brasileiro Psiq*., 2010; 59, 58–64.
38. Williams CL, Tappen RM. Exercise training for depressed older adults with Alzheimer's disease. *Aging Mental Health*, 2008; 12: 72-80.
39. Overshott R, Burns A. Treatment of dementia. *J Neurol Neuros Psychiatry*, 2005; 76: 53-59.
40. Eggermont LHP, Scherder EJA. Physical activity and behaviour in dementia: a review of the literature and the implications for psychosocial. *Dementia,* 2006; 5: 411-428.
41. Lai CK, Chi I, Kayser-Jones J. A randomized controlled trial of a specific reminiscence approach to promote the well-being of nursing home residents with dementia. *Int Psychogeriatr.*, 2004;16:33–49.
42. Haslam C, Haslam SA, Jetten J, et al. The social treatment: the benefits of group interventions in residential care settings. *Psychol Aging*, 2010; 25: 157-167.
43. Politis AM, Vozzella S, Mayer LS, et al. A randomized, controlled, clinical trial of activity therapy for apathy in patients with dementia residing in long-term care. *Int J Geriatr Psychiatry*, 2004; 19:1087–94.
44. Woods B, O'Philbin L, Farrell EM, Spector AE, Orrell M. Reminiscence therapy for dementia. *Cochrane Data Syst Rev*., 2018; 3. Art. No.: CD001120.
45. Lai C. The merits and problems of Neuropsychiatric Inventory as an assessment tool in people with dementia and other neurological disorders. *Clin Interv Aging*, 2014; 9: 1051-1061.