

Non-pharmacological interventions for agitation/aggressive behaviour in patients with dementia: a randomized controlled crossover trial

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Summary

Agitation/aggressive behaviour is a common behavioural and psychological symptom in people with dementia (PwD), occurring with a frequency of between 13-50.4% according to recent studies, and the rate increases as the severity of cognitive decline increases.

The burden on caregivers is considerable.

This trial is a randomized controlled crossover trial conducted in Greece.

The following measures were used: the Mini-Mental State Examination, Addenbrooke's Cognitive Examination Revised, Geriatric Depression Scale, Functional Rating Scale for Symptoms in Dementia and Neuropsychiatric Inventory.

According to the results the most effective non-pharmacological intervention for reducing agitation/aggressive behaviour in PwD was music therapy, followed by aromatherapy and massage, and finally physical exercise.

KEY WORDS: aggressive behaviour, agitation, BPSD, dementia, non-pharmacological treatments, randomized trial.

Introduction

Non-pharmacological approaches play an important role in the management of the behavioural and psychological symptoms of dementia (BPSDs). BPSDs affect approximately 90% of patients with dementia (PwD), in whom the condition may range from the mild cognitive impairment (MCI) stage to severe dementia (Gitlin et al., 2012). Nowadays there are several pharmacological treatments used in order to reduce BPSDs, but no medication has been approved by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA). In particular, further research is needed to evaluate the efficacy of cholinesterase inhibitors in the treatment of BPSDs. Anti-psychotic drugs, although sometimes used, are mainly avoided, because of their side effects. Indeed, these drugs have numerous and serious side effects, including dyskinesia, extrapyramidal symptoms, osteoporosis, orthostatic hypotension, increased risk of falls, increased risk of cerebrovascular accidents, metabolic disorders, neutropenia, seizures and weight gain (Kales et al., 2012). Furthermore, antidepressants, such as selective serotonin reuptake inhibitors (citalopram, trazodone), have been found to be effective in reducing agitation in PwD and in decreasing the burden on family caregivers (Porsteinsson et al., 2014). In addition, benzodiazepines should be avoided because they cause sedation, cognitive decline, falls, drug dependence, dizziness and withdrawal reactions (Tampi and Tampi, 2014). Moreover, mood stabilizers, such as carbamazepine, gabapentin, lamotrigine and topiramate, either show many side effects, including hyponatremia, cardiac toxicity, Stevens-Johnson syndrome and sedation, or need further research (Wang et al., 2015).

Agitation/aggressive behaviour is a common BPSD in PwD and can appear either in the MCI stage, or in the early or moderate and severe stages of dementia. The frequency of agitation/aggressive behaviour is between 13 and 50.4% according to recent studies, and the rate increases as the severity of the cognitive decline increases (Millan-Calenti et al., 2016). It is difficult to treat as patients often refuse to take their drugs. The burden on caregivers is considerable, as they can struggle to handle these patients and/or can sometimes even be hurt by them. Nowadays, there are several promising non-pharmacological interventions for reducing this agitation/aggressive behaviour, such as cognitive stimulation, physical exercise, aromatherapy, massage therapy, bright light therapy, music therapy and multisensory stimulation.

The aim of the present study was to evaluate three non-pharmacological interventions for agitation/aggressive behaviour in PwD. In order to achieve this we designed a randomized controlled crossover trial including sixty (n=60) participants with different types of dementia.

Materials and Methods

Subjects

In this study, we included sixty (n=60) patients from the Neurological Department of the “G. Gennimatas” General Hospital of Athens, Greece. The patients were diagnosed with several types of dementia: Alzheimer’s disease, vascular dementia (VaD), frontotemporal dementia (FTLD), Parkinson’s disease dementia (PDD), mixed dementia, dementia due to AIDS. We also included patients with mild cognitive impairment.

Table I shows the demographic characteristics of the sample and the baseline measures: 51.7% were women (31 patients) and 48.3% were men (29 patients). The average age of the participants was 72.3 years (mean 72.3, SD 8.4), and their average duration of education was 9.43 years (mean 9.43, SD 4.43).

Procedure

In order to evaluate 3 non-pharmacological interventions for the reduction of agitation/aggressive behaviour in dementia a randomized controlled crossover trial was designed. The Neuropsychiatric Inventory (NPI) (Cummings et al., 1994; Politis et al., 2004) was used; this questionnaire was administered, by the clinician, to the family caregiver at the start of the procedure. The patients were randomly assigned to 6 different groups. In order to have reliable results the sequence of the interventions (A, B and C) varied. Table II shows the sequence of the interventions. Each intervention lasted 5 days. On the last 2 days of each week, no treatment was used. At the end of every week, the NPI questionnaire was administered, always by the same clinician and to the same family caregiver as at the beginning.

Interventions

A) Physical exercise

Family caregivers preferred walking as the easiest form of exercise.

According to one large review (which included 10 other reviews and 6 research articles) (Thune-Boyle et al., 2012), most trials used activities such as: walking, sport activities, aerobics, exercises for strength, balance and flexibility, sit-to-stand repetitions, cycling and so on. However, walking seems to have been the activity used in most studies, sometimes on its own and sometimes in combination with another activity (such as aerobics) (Eggermont et al., 2006). With regard to the duration of the exercise, the review mentions that most studies were unable to indicate a specific time, whereas others provided details of the frequency and duration (Heyn et al., 2004). It has been reported that 30-45’ minutes of exercise three times a week can be beneficial (Edwards et al., 2008; Thune-Boyle et al., 2012; Fleiner et al., 2017). According to the review, a higher frequency of exercise is related to better results.

B) Massage and aromatherapy

Aromatic oils, such as lavender, *Melissa officinalis* and lemon balm were used for the current treatment. The therapeutic effects of the above-mentioned oils have been mentioned in other trials as well (Maggio et al., 2016). To date, the literature has shown massage and aromatherapy to provide promising results (Legere et al., 2017).

We used 60 drops of the oils and the massage was given every night before bedtime. Each session lasted 20 minutes, during which the patient’s back, arms, hands and wrists were massaged, as in most of the trials in a large review (Forrester et al., 2014).

C) Music therapy

Table I - Demographic characteristics of the total sample.

	Age	Education	MMSE	ACE-R	GDS	FRSSD	NPI Aggressive behaviour	NPI Caregiver distress
Mean	72.35	9.43	19.72	58.33	8.47	15.75	7.47	3.45
N	60	60	60	60	60	60	60	60
Std. deviation	8.489	4.435	4.469	16.343	5.347	9.032	1.761	.832

Abbreviations: MMSE=Mini-Mental State Examination; ACE-R= Addenbrooke’s Cognitive Examination Revised; GDS=Geriatric Depression Scale; FRSSD= Functional Rating Scale for Symptoms in Dementia, NPI=Neuropsychiatric Inventory

Table II - The sequence of the procedures in the 6 groups.

Group	Sequence	1st week	2nd week	3rd 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

Music therapy has shown promising results in reducing agitation. However, even though it is still not known what type of music and how much time is needed, there are trials which have mentioned beneficial effects (Ueda et al., 2013). In the current study, the caregivers chose the patients' favourite music. According to a recent review, patients can benefit from listening to their preferred music for 30-50 minutes per day for 2-3 days in the course of a week (Craig, 2016). The current study followed the same duration, but for 5 days.

Measures

Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al., 1975; Fountoulakis et al., 2000) is a 30-point questionnaire that is used to evaluate cognitive impairment and 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)

The ACE-R (Mathuranath et al., 2000; Konstantinopoulou et al., 2011) is a 100-point questionnaire that is used to evaluate cognitive impairment. It includes the MMSE. It is highly sensitive and can be used for the diagnosis of dementia. It includes questions about orientation, registration, attention, concentration, recall, verbal fluency, memory, language, visuospatial abilities, perceptual abilities and recognition. Higher scores indicate better cognitive performance.

Geriatric Scale of Depression (GDS)

This scale (Yesavage et al., 1983; Fountoulakis et al., 1999) is a 30-item questionnaire that examines whether a patient has depression. The patient answers with a YES/NO. Higher scores indicate higher levels of depression.

Functional Rating Scale for Symptoms in Dementia (FRSSD)

This scale (Tsolaki, 1997; Hutton et al., 1998) is used to assess daily functioning ability. It includes 14 daily activities and it is scored from 0 to 3 (0= fully independent and 3= fully dependent on the caregiver).

Neuropsychiatric Inventory (NPI)

The NPI questionnaire (Cummings et al., 1994; Politis et al., 2004) is administered to the caregiver. It includes questions for 12 behavioural and psychological symptoms in dementia with 7-8 sub-questions for each. These 12 symptoms are: delusions, hallucinations, aggressive behaviour, depression, anxiety, euphoria, apathy, disinhibition, agitation, wandering, sleeping disturbances and eating problems.

The questionnaire evaluates the frequency and severity of the symptom as well as the impact that each behaviour has on the caregiver. Frequency is scored from 0 to 4 (0= rarely happens, 4= happens every day), severity from 1 to 3 (1=mild severity, 3=severe), and distress from 0 to 5 (0= not at all, 5= extremely). The domain total score is the product of: a) the frequency X the severity score, and b) the total caregiver distress score. A final total score is obtained by summing all the domain total scores.

Data analysis

Categorical variables were presented as percentages while continuous variables were presented as mean values (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's least significant difference 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.

Results

The study sample comprised sixty (n=60) participants, of whom 63.3% suffered from AD, 3.3% from VaD, 15% from PDD, and 3.3% from FTLD; 13.3% had MCI and 1.7% had dementia due to AIDS. The mean scores of the measures were as follows: MMSE 19.7 (SD 4.4), ACE-R 58.3 (SD 16.3), GDS 8.4 (SD 5.3), FRSSD 15.7 (SD 9), NPI 7.4 (SD 1.7) and NPI caregiver distress 3.4 (SD 0.8). As mentioned, the NPI gives two scores: the first is the result of the frequency score multiplied by the severity score of the behaviour, and the second score indicates the impact (in terms of distress) of the behaviour on the caregiver.

The GLM results showed positive effects of the music therapy intervention. Specifically, the NPI score after music therapy (mean, SD= 5.15, 1.45) was significantly lower than after physical activity (6.9, 2.11, $p=0.003$) and aromatherapy and massage therapy (6.1, 1.75, $p=0$).

The same treatment had a significant result effect on caregiver distress ($p<0.001$). Distress was significantly lower after music therapy (2.23, 0.83) than after aromatherapy and massage therapy (3.13, 0.89, $p=0.45$), and physical activity (2.75, 0.79, $p=0$). No post-intervention difference in NPI was found between the different groups ($p=0.022$) in relation to the timing of the treatment. Table III shows the descriptive statistics, between the different interventions, for NPI and distress after the treatments (post-treatment results).

Discussion

Agitation/aggressive behaviour can be divided into 3 subtypes: physically non-aggressive behaviour, aggressive behaviour, and verbally agitated behaviour. According to the NPI (Cummings et al., 1994; Politis et al., 2004), the most common aggressive behaviours are manifested when the patient gets upset when others try to help him/her in activities of daily living (such as bathing or changing clothes); wants things done his/her own way; is uncooperative; displays behaviours that are difficult to handle, e.g., shouts, makes loud noises, slams doors, throws things, attempts to hurt others, etc. According to the results of the present study, the most effective non-pharmacological intervention for the reduction of agitation/aggressive behaviour in PwD was

Table III - Descriptive statistics between the different interventions for NPI and distress after the treatment.

	Physical Exercise	Massage & Aroma	Music	Distress (Physical Exercise)	Distress (Massage & Aroma)	Distress (Music)
Mean	6.15	6.90	5.15	2.53	3.13	2.23
N	60	60	60	60	60	60
Std. deviation	1.755	2.113	1.459	.791	.892	.0831

the music therapy. The second most effective intervention was the aromatherapy and massage, and the third the physical exercise.

Specifically, physical exercise seems to show promising results. There are several studies that confirm the positive results of exercise (Overshott et al., 2004; Volicer et al., 2006; Aman and Thomas, 2009). More than a few studies seem to have found some positive results after months of exercising, but these results did not last for a long period of time (Thune-Boyle et al., 2012). As mentioned, according to our results, exercise was the third most effective intervention.

The results of the music therapy intervention in the present study are consistent with the literature. Positive results have been shown in previous randomized controlled trials (Svansdottir and Snaedal, 2006; Garland et al., 2007; Lin et al., 2011; Gerdner, 2012; Vink et al., 2013) and there are several reviews that confirm these results (Sung et al., 2012; Blackburn and Bradshaw, 2014). One possible explanation for the very positive results of music therapy in terms of reducing agitation could be that music can influence attention and elicit positive memories from the patient's earlier life, which would help to decrease agitation. Furthermore, music therapy was the most effective non-pharmacological intervention not only for the PwD, but also for reducing caregiver distress.

Massage therapy and aromatherapy emerged as the second most effective non-pharmacological intervention for reducing agitation in PwD. According to previous randomized controlled trials, massage and aromatherapy can be beneficial in terms of reducing agitation/aggressive behaviour (Woods and Dimond, 2002; Lin et al., 2007; Burns et al., 2011), however it is crucial to report note that some PwD, and in particular patients with PDD and Alzheimer's dementia, may suffer from anosmia and this is something that may lead to analytical bias (Storch et al., 2015).

The small sample size, the fact that each intervention lasted only one week, and the absence of follow-up are some of the limitations of the current study. Therefore, our results may be ambiguous for future research. Future work should focus more on non-pharmacological interventions for reducing agitation and BPSDs in general, as the current pharmaceutical treatments are expensive and have serious side effects. There is a strong need for further research and randomized controlled trials in order to confirm the beneficial effects of the various non-pharmacological interventions. Double-blinded trials could be of help and emphasis should be placed on the duration of the positive effects, because it is crucial to establish how long they last. In addition, as dementia is a complex disease, a combination of non-

pharmacological and pharmacological treatments seems preferable.

In conclusion, it seems that non-pharmacological interventions should be the first-line treatment for the management of some BPSDs, because current drugs can have some very serious side effects.

Furthermore, agitation is a very common behaviour in PwD in all stages (from MCI to severe dementia) and all types of dementia. It can affect 30% of PwD and is associated with a poorer quality of life and an increased caregiver burden. In fact, it is one of the most common reasons why family caregivers decide to institutionalize these patients. In short, the presence of BPSDs in PwD continues to be a serious problem that needs further research.

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