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Research paper

Effects of frequent and long-term exercise on neuropsychiatric symptoms in patients with Alzheimer's disease – Secondary analyses of a randomized, controlled trial (FINALEX)☆

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ABSTRACT

Background: Neuropsychiatric symptoms (NPS) are common in Alzheimer's disease (AD) and are associated with admission to institutional care. Current guidelines recommend non-pharmacological interventions as the first-line treatment for NPS. However, high-quality randomized studies focused on NPS are scarce. The objective here was to examine whether a regular and long-term exercise programme either at home or as a group-based exercise at an adult day care centre has beneficial effects on AD patients' NPS or permanent institutionalizations.
Design, setting, and participants: A randomized, controlled trial with 210 community-dwelling AD patients.
Intervention: Two types of intervention comprising (1) group-based exercise in day care centres (GE) and (2) tailored home-based exercise (HE), both twice a week for 12 months, were compared with (3) a control group (CG) receiving usual community care.
Measurements: NPS were measured with the Neuropsychiatric Inventory (NPI) at baseline and 6 months, and depression with the Cornell Scale for Depression in Dementia (CSDD) at baseline and 12 months. Data on institutionalizations were retrieved from central registers.
Results: No significant differences between the groups were detected in NPI at 6 months or in CSDD at 12 months when analyses were adjusted for age, sex, baseline Clinical Dementia Rating, and Functional Independence Measure. There was no difference in admissions to permanent institutional care between the groups.
Conclusions: Regular, long-term exercise intervention did not decrease NPS in patients with AD.

1. Introduction

Neuropsychiatric symptoms (NPS), such as agitation, anxiety, depression, and delusions, are common in patients with Alzheimer's disease (AD) and are considered clinically as significant as the other core symptoms; cognitive and functional decline. NPS are often associated with a lower quality of life, higher caregiver distress, poor prognosis, earlier institutionalization, and increasing health care costs [1,2]. Of patients with dementia, 80–90% suffer from these symptoms at some point during disease progression [3,4]. In the MAASBED longitudinal study, 65% of dementia patients with NPS at baseline continued to have at least one symptom during the two-year follow-up [3]. Occurrence of the NPS may be persistent or intermittent, complicating their prevention and treatment.

Researchers have suggested that NPS in dementia can be divided into clusters of symptoms or subsyndromes that may differ

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in prevalence, course over time, or pathophysiology [5,6]. Although minor differences in the studies exist, definitions of the subsyndromes of hyperactivity, mood, and psychosis are in general agreement and supported by clinical evidence [4–6]. Treatment interventions may be more beneficial when targeting subsyndromes rather than individual symptoms [5].

Traditionally, psychotropic medication, especially antipsychotic drugs, has been used to alleviate NPS. However, the benefits are often modest and must be carefully weighed against the risk of adverse effects [7,8]. Current guidelines recommend non-pharmacological methods as the first-line treatment approach for NPS (Nice guideline 2016). The non-pharmacological treatments comprise various behavioural, environmental, and care giver supportive interventions. Evidence supporting beneficial treatment effects of these therapies has been accumulating during recent years. Still, high-quality randomized studies on non-pharmacological treatments strategies for NPS in AD are few [9].

Over the last decades a considerable amount of evidence has accumulated of the effects of exercise as preventive or even disease-modifying treatment of age-related dementia. The positive effects are thought to be mediated through improvement of cerebrovascular circulation, stimulation of angiogenesis and neurogenesis, and controlling the inflammation processes [10].

It is also possible that such mechanisms as improved well-being and self-esteem, as well as increased social contacts may generate symptomatic relief as a result of exercise in dementia patients [11].

Physical exercise may improve mood and sleep and reduce depressive symptoms in healthy older adults [12,13]. Moreover, a physically active lifestyle in dementia patients has been shown to be associated with a lower frequency of NPS [14]. However, findings of the effects of exercise intervention on NPS in dementia patients from clinical studies and meta-analyses have so far been inconsistent [15,16]. Positive effects of exercise have been found to be more pronounced in some symptoms (depression, agitation, wandering, sleep) than in others (anxiety and apathy) [17]. According to a recent meta-analysis, depression and aberrant motor behaviour appear to be the NPS most positively affected by exercise. However, the effects on global NPI scores have been insignificant [15]. A substantial heterogeneity has been found in the types of exercise used in the intervention studies; aerobic, resistance training and mixed exercise being the most widely used. Recent Cochrane review was not able to give a recommendation of what type of exercise, or at what frequency or duration would the most beneficial for patients with dementia [16].

The objective of this study was to examine whether regular, long-term exercise has beneficial effects on depression and other NPS in patients with AD. We also examined the impact of exercise on admissions to permanent institutional care.

2. Methods

2.1. Study design

This paper reports secondary findings of a randomized controlled study, FINALEX, which examined the effects of exercise intervention on AD patients' physical performance, cognition, and NPS [18]. Community-dwelling older adults with AD were randomly allocated into two intervention groups or a control group. The exercise sessions were administered by a physiotherapist either at participants' homes (home-exercise group, HE) or at day care centres (group-exercise group, GE) for 60 minutes twice a week for 12 months. The controls (CG) continued with normal community care. The study protocol was approved by the Ethics Committee of Helsinki University Central Hospital. A detailed description of the design and endpoints of the FINALEX study has been provided earlier [18].

This article evaluates the effects of exercise on NPS, depression, and institutionalizations in AD patients.

2.2. Participants

Patients over 65 years of age living with a spouse in the Helsinki area and who were listed on the AD drug reimbursement register of the Social Insurance Institution of Finland were invited to participate in this trial. Patients in this register are diagnosed with AD according to the NINCD-ADRDA criteria [19] evaluated by a geriatrician/neurologist.

Individuals showing an interest in participating were assessed for additional inclusion criteria: ability to walk independently with or without a mobility aid, no terminal illness, and at least one sign of frailty (one or more falls during the last year, decreased walking speed, or unintentional weight loss). Altogether 210 patient-carer dyads fulfilled all inclusion criteria and were enrolled in the study. Each participant and spousal care giver gave informed, written consent. If the patient's judgement capacity was reduced, the spouse provided consent on behalf of the patient. All patients randomized into one of the exercise groups underwent a thorough medical examination by a geriatrician to ensure safety of the intervention.

2.3. Measures

We used the Neuropsychiatric Inventory (NPI) to assess NPS. The NPI evaluates 12 neuropsychiatric disturbances frequently seen in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, and appetite and eating abnormalities. For each symptom, the severity is multiplied by the frequency, with the summed score providing the total NPI score. The score ranges from 0 (no NPS) to 144 (the highest number and most severe symptoms). The validity and reliability of NPI have been established, and it has also been found to be fairly sensitive [20]. A trained nurse administered the NPI to the spousal informant at baseline and 6 months.

In addition to NPI scores, we investigated the effects of intervention on behavioural subsyndromes. We categorized the individual symptoms into subgroups of "Hyperactivity" (agitation, aggressiveness, disinhibition, irritability, aberrant motor behaviour), "Mood and apathy" (depression, anxiety, euphoria, apathy, sleeping problems, eating problems), and "Psychosis" (hallucinations, delusions) according to Aalten and co-workers [5].

We evaluated depressive symptoms with the Cornell Scale of Depression in Dementia (CSDD) [21] at baseline and 12 months. In CSDD, the information is obtained by interviewing the caregiver and by observing and interviewing the patient. The scale contains 19 items with a maximum score of 38 and a score > 10 indicating depression. This scale has good sensitivity and specificity and has been validated in populations of dementia patients [22].

The stage of dementia was assessed with Clinical Dementia Rating [23], and the Charlson Comorbidity Index [24] was calculated to measure the overall disease burden. At baseline, the demographic data and medical history were collected.

Evaluations of physical functioning were done with Functional Independence Measure (FIM), and cognition with Mini Mental Stage Examination. The participants were followed for two years for use of nursing homes. Data on admissions to permanent institutional care were retrieved from central registers.

2.4. Randomization

The participants were randomized after the baseline visit. A separate randomization centre was used to assign the patient-spouse dyads ($n = 210$) into three groups of equal size ($n = 70$):