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# Role of physical activity in ameliorating neuropsychiatric symptoms in Alzheimer disease: A narrative review

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**Objective:** Neuropsychiatric symptoms (NPs) affect almost all patients with Alzheimer disease (AD). Because of the complications associated with the pharmacological treatment, nonpharmacological treatment (such as physical activity) can be considered as an additional complementary treatment option for NPs. The aim of this review is to evaluate the impact of physical activity on NPs in patients with AD.

**Methods:** We searched Pubmed and Google Scholar for potential eligible articles until March 1, 2018.

**Results:** Although there are contradictory results showing the impact of physical exercise on NPs, most of them reported that it had a significant effect on depression and sleep disturbances in patients with AD. The beneficial effects could be explained through several mechanisms, including modulated production of neurotransmitters; increasing neurotrophins, such as brain-derived neurotrophic factor; reduction of oxidative stress and inflammation; elevation of cerebral blood flow; hypothalamic pituitary adrenal axis regulation; and support of neurogenesis and synaptogenesis. Physical activity can also improve cardiovascular risk factors, which may exaggerate NPs. There is limited evidence for other NPs such as agitation, disinhibition, apathy, hallucinations, and anxiety.

**Conclusion:** Physical activity may ameliorate depression and sleep disturbances in patients with AD. Therefore, physical activity can be a "potential" add-on treatment to drugs to reduce or prevent these symptoms onset and recurrence in patients with AD. However, further studies are needed to focus on relationship between physical activity and other NPs.

KEYWORDS

Alzheimer disease, neuropsychiatric symptoms, physical activity, physical exercise

## 1 | INTRODUCTION

As global population becomes older, one of the most common chronic health conditions is Alzheimer disease (AD).[1] That means that not only AD but also the burden it brings to families, caregivers, health-care systems, and governments will increase in the next future. In addition to cognitive impairment, neuropsychiatric symptoms in dementia are among the strongest causes of the burden and often occur as a result of deterioration in mood, thought, perception, and behavior.[2] These symptoms have been traditionally divided into 4 clusters: hyperactivity cluster (agitation, aggression, euphoria, disinhibition, irritability, and aberrant motor activity), psychosis cluster (hallucinations and delusions), mood liability cluster (depression and anxiety), and instinctual cluster (appetite disturbance, sleep disturbance, and apathy),[2] and they pave the way for long-term hospitalization, accelerated disease progression, dependence on activities of daily living, decreased quality of life, increased mortality, and cost of care.[3] Several previous studies found that NPs

  

are more closely related to caregiver burden than other symptoms, such as deteriorated cognitive function or limitations in the activities of daily living,[4,5] and caregivers of the patients with NPs are more vulnerable.[6] One or more of NPs can affect approximately 97% of patients with AD during the course of the disease.[3,7] A recent study also demonstrated that the prevalence of having at least 1 NPs among patients with mild cognitive impairment (MCI) and mild to moderate dementia was 74% and 85%, respectively.[8] When these high ratios are considered, it is clear that preventing or at least treating NPs is very important in patients with AD. However, dealing with NPs is very complex for both health care professionals and families.

Although currently pharmacological therapies (such as antidepressants, antipsychotics, anxiolytics, anticonvulsants, and cholinesterase inhibitors) are used to reduce the frequency and severity of NPs when nonpharmacological interventions are ineffective, they provide only moderate symptoms control in most of the patients.[9,10] Additionally, they have serious adverse effects (eg sedation, postural hypotension, metabolic syndrome issues and electrolyte changes, drug interactions, cardiac arrhythmia, extrapyramidal symptoms, and falls).[10-13] Because of the complications associated with the pharmacological treatment, current guidelines recommend that nonpharmacological interventions should be attempted first, followed by the least harmful medication for the shortest time possible time.[14] Therefore, new interventions, added to drug therapy, are considered a potential alternative treatment to reduce or prevent NPs onset and recurrence. Potential nonpharmacological options traditionally include aromatherapy, multisensory stimulation, therapeutic use of music, animal-assisted therapy, and massage that is particularly useful for middle-to-late stages of dementia, while physical activity is probably more useful in early to middle stages.[15]

Among nonpharmacological interventions, physical activity seems to be the most promising candidate. Physical activity can reduce the risk or delay the onset of AD[16] and has a positive effect on cognitive flexibility, depressive symptoms, cardiovascular health, sleep (REM sleep behavior disorder), and general wellness, which are predictors for ongoing neurodegenerative process in patients without dementia[17,18]; it can also improve cognitive functions and NPs in patients with dementia, and the role of physical activity is a novel area of research in dementia, in particular in AD.[19-22] Furthermore, many geriatric syndromes may also be prevented by reducing NPs.[23] However, there is a limited number of studies upon the effect of physical activity on NPs, of which the results are conflicting.[19-21] Therefore, this review is aimed to explain the current literature and the effects of physical activity on NPs in patients with AD and to raise awareness about this issue.

## 2 | METHODS

We searched Pubmed and Google Scholar for potential eligible articles until March 1, 2018. We included all articles on physical exercise and/or physical activity in the treatment of NPs in people affected by AD. Studies were excluded if they did not include only patients with AD.

**Key points**

- Physical activity has a positive effect on cognitive flexibility, depressive symptoms, cardiovascular health, and general wellness which are predictors of AD.
- Physical activity can ameliorate depression and sleep disturbances in patients with AD.
- Physical activity can be considered as potential add-on treatment to drugs to reduce or prevent some NP onset and recurrence, with no serious side effects and many proven health benefits.

We screened for the concepts of physical exercise and physical activity associated with the most common NPs in AD, ie, agitation/aggression/euphoria/ disinhibition/irritability/ aberrant motor activity/hallucinations/delusions/psychosis/depression/ anxiety/appetite disturbance/sleep disturbance/apathy.

We finally included papers known to the authors on the topic (academics and clinical experts in the field), and we reviewed the references lists of all included papers. Priority was given to systematic reviews (with or without meta-analyses), followed by randomized controlled trials, observational studies, and to expert guidelines, without excluding any paper for its nature.

## 3 | DOES PHYSICAL ACTIVITY REDUCE NPS?

The main characteristics of the studies exploring physical activity and exercise in AD are reported in Table 1. Several studies have investigated whether physical activity may have beneficial effects on depression. One of them showed that lack of physical activity was an independent predictor of depression in patients with AD.[28] In a randomized controlled trial (RCT) study, Vreugdenhil et al found in a sample of community-dwelling adults with AD that performing a home-based exercise program including daily strength-balance exercises and 30 minutes of brisk walking resulted in a significant reduction in depression score compared with a control group.[34] In another RCT by Teri et al, 153 patients with AD were randomly allocated to an exercise intervention group (n = 76) or a control group (n = 76). The intervention group conducted moderate intensity exercise with aerobic/endurance activities, strenght training, balance, and flexibility training for 12 weeks. The intervention resulted in a significant reduction in depression.[32] Williams and Tappen randomized 45 nursing home residents, with moderate-to-severe AD, into 3 groups: the first included a 16-week program of comprehensive exercise (strength, flexbility, balance, and supervised walk), one only supervised walking and the third one social conversation. Reduced depressive symptoms were observed in all 3 groups with some evidence of superior benefit of exercise.[35] Yu et al, similarly reported that individualized moderate intensity cycling 3 times a week for 6 months reduced patients' depression.[36] A study of Stella et al, found that performing aerobic activity for 60 minutes, as well as exercises to improve felxibility,

**TABLE 1** Effect of physical activity on neuropsychiatric symptoms in people affected by Alzheimer disease

| Author, Year | Type of Study | Sample Size | Mean Age (SD) | Type of Physical Exercise | Frequency | Main Findings |
|---|---|---|---|---|---|---|
| Hoffmann et al, 2016 [24] | RCT | 200 patients with mild AD<br>Exercise: 107<br>Control: 93 | Exercise group 69.8 ± 7.4<br>Control group 71.3 ± 7.3 | Moderate-to-high intensity aerobic exercise | 60-min sessions 3 times a week for 16 weeks | Significant reduction in NPs in patients with mild AD |
| Kurz et al, 2009[25] | RCT | Community dwelling Exercise group (10 patients with AD and 18 patients with MCI)<br>Control group = 12 patients with MCI) | MCI control 70.8 ± 6.9<br>MCI intervention 70.4 ± 8.4<br>AD intervention 66.0 ± 8.7 | Activity planning, self-assertiveness training, relaxation techniques, stress management, use of external memory aids, memory training, and motor exercise | 3 hours/week for 4 weeks | Significant improvement in ADL, verbal memory, and reduction in depression in patients with MCI, but not in patients with AD |
| McCurry et al, 2011[26] | RCT | 132 patients with AD and their in-home caregivers<br>Walking group: 32<br>Light group: 34<br>Combination group: 33<br>Control group: 33 | Walking group 82.2 ± 8.5<br>Light group 80.6 ± 7.3<br>Combination group 80.0 ± 8.2<br>Control group 81.2 ± 8.0 | A caregiver-supervised, self-paced walking program | 30 continuous minutes/day ≥4 days a week for 6 months | Significant improvements in total wake time and better sleep efficiency intervention groups compared with control group |
| Nascimento et al, 2014[27] | RCT | Patients with AD<br>Exercise group: 19<br>Control group: 16 | Exercise group 76.8 ± 6.8<br>Control group 77.9 ± 5.9 | Multimodal exercise program (warm up, muscular resistance, balance and motor coordination, and aerobic fitness) | Three 1-hour sessions per week, for 6 months | Significant improvements in sleep disturbances in exercise group and maintenance or worsening in control group |
| Regan et al, 2005[28] | Cross-sectional | 224 community-based patients with AD<br>Depressed patients = 51<br>No depressed patients = 173 | 81.0 | Participants were divided into absent, moderate (regular walks or gardening), or vigorous exercise (aerobics classes or ballroom dancing) | NA | Lack of exercise was an independent predictor of depression |
| Rolland et al, 2007[29] | RCT | 132 patients with mild to severe AD of 5 different nursing homes<br>Exercise group = 67<br>Control group = 67 | Exercise group 82.8 ± 7.8<br>Control group 83.1 ± 7.0 | Collective exercise program (walk, strength, balance, and flexibility training) | 1 hour/twice weekly, for 12 months | Significantly slower decline of ADL in exercise group<br>No significant training effects on behavioral disturbances and depression |
| Shih et al, 2017[30] | Cross-sectional | 184 patients with AD | 78.5 ± 7.6 | Walking | Walking time period | Longer weekly duration of walking is associated with better the sleep quality and less sundown syndrome |
| Steinberg et al, 2009[31] | RCT | 27 randomized home-dwelling adults patients with AD<br>Exercise group = 14<br>Control group = 13 | Exercise group 76.5 ± 3.9<br>Control group 74.0 ± 8.1 | Aerobic exercises program (flexibility, strength, and balance) | Daily, for 12 weeks | A trend for improved performance on functionality but increasing depression scores in the exercise group |

(Continues)

**TABLE 1** (Continued)

| Author, Year | Type of Study | Sample Size | Mean Age (SD) | Type of Physical Exercise | Frequency | Main Findings |
|---|---|---|---|---|---|---|
| Stella et al, 2011[38] | RCT | Community-dwelling patients with AD and their caregivers<br>Exercise group = 16<br>Control group = 16 | 77.8 ± 5.8 | Aerobic exercises (flexibility, strength, and agility) and functional balance exercises | 60 minutes 3 times per week, for 6 months | Significant reduction in neuropsychiatric conditions, depression, and caregiver's burden in exercise group |
| Teri et al, 2003[32] | RCT | Community-dwelling adults with AD<br>Exercise group = 76<br>Control group = 76 | Exercise group = 78 ± 6<br>Control group = 78 ± 8 | Moderate intensity exercise with aerobic/endurance activities, strength training, balance, and flexibility training | 2 sessions per week for the first 3 weeks, followed by weekly sessions for 4 weeks and biweekly sessions over the next 4 weeks of 30-minute duration | Significant decrease in depression and a trend for less institutionalization due to NPs in the exercise group |
| Venturelli et al, 2016[33] | RCT | 80 patients with AD<br>Aerobic exercise = 20<br>Cognitive training group = 20<br>Combination group = 20<br>Controlgroup = 20 | Aerobic exercise<br>84 ± 7<br>Cognitive T. group<br>86 ± 9<br>Combination group<br>85 ± 8<br>Control group:<br>84 ± 10 | Walking at moderate intensity | 5 days/week, 1 hour before sunset, for 3 months | Improvement in NPs, agitation, and sundowning syndrome symptoms in aerobic exercise |
| Vreugdenhil et al, 2012[34] | RCT | Community-dwelling adults with AD and their caregivers<br>Exercise group = 20<br>Control group = 20 | 74.1 | Home-based exercise program of daily exercises and walking under the supervision of their caregiver | At least 30 minutes a day, for 12 weeks | A trend for improvement for those who exercised on measures of depression and caregiver burden |
| Williams and Tappen, 2008[35] | RCT | 45 nursing home residents with moderate-to-severe AD<br>Three interventional groups were comprehensive exercise, supervised walking, and social conversation | 87.9 ± 5.95 | Group 1: comprehensive exercise (strength, flexibility and balance, and supervised walk)<br>Group 2: supervised walking;<br>Group 3: social conversation | Exercise 5 times per week with the duration of 30 minutes, for 16 weeks | Significant decrease in depression and improved mood in all 3 treatment groups |
| Yu et al, 2013[36] | Open-label study (one group) | Community-dwelling adults with mild-to-moderate AD.<br>Exercise group = 11 | 81.4 ± 3.6 | Individualized moderate intensity cycling | 3 times a week (10 to 45 minutes per session) over 6 months | Linear decrease in depression over time |
| Yu et al, 2015[37] | Open-label study (one group | Community-dwelling older adults with mild-to-moderate AD n = 26 | 78 ± 8 | Aerobic exercise (moderate intensity cycling intervention) | Progressively increased by 5-minute increments from 15 minutes initially to 45 minutes per session over 6 months | No changes in NP severity but significant reduction in caregiver distress |

Notes: AD, Alzheimer disease; ADL, activity daily living; MCI, mild cognitive impairment; NA, not available; NPs, neuropsychiatric symptoms; RCT, randomized controlled trial.

strength, and functional balance over 6 months in home-dwelling patients, led to a reduction in depression and caregiver burden.[38] Another RCT published by Hoffman et al revealed that moderate-to-high intensity aerobic exercise could decrease Neuropsychiatric Inventory scores in patients with mild AD.[24]

On the other hand, several studies have investigated whether physical activity may have beneficial effects on sleep disturbances in patients with AD. In an RCT by McCurry et al, patients with better adherence to walking (≥4 d/wk) had significantly less total wake time and better sleep efficiency.[26] Similarly, Shih et al also demonstrated that the longer the weekly duration of walking is linked to better the sleep quality, the less sundown syndrome.[30] Nascimento et al found that 3 one-hour sessions per week of a multimodal exercise program for 6 months improved sleep disturbances in exercise group, compared with a control group.[27]

Lastly, in a study by Venturelli et al, walking at moderate intensity could reduce agitation as well as sundowning syndrome symptoms in patients with AD.[33]

However, positive effects of exercise were not consistently shown by all studies.[31] In a study by Kurz et al, community-dwelling adults with MCI or AD treated with cognitive rehabilitation program including motor exercises 3 hours a week for 4 weeks, experienced significant reduction in depression and improved activities of daily living in patients with MCI, but not in patients with AD.[25] The null effect in patients with AD was explained by difficulty in performing some components of the exercise program which were linked to the cognitive abilities of this group. Rolland et al carried out a study where exercise was performed by 132 patients with mild-to-severe AD 1 hour/twice weekly; there were no significant effects on NPs and depression, likely owing to the low levels of activity performed.[29] Another study by Yu et al carried out a moderate intensity cycling intervention and found that it did not change NP severity, but there was signitificant reduction in caregiver distress.[37] Additionaly, Steinberg et al divided 27 patients with AD into intervention (n = 14) and control groups (n = 13). The intervention group received a daily program of aerobic, balance and flexibility, and strength training; a trend toward increasing depression scores was found in the exercise group.[31] Therefore, exercise in AD may be associated, at least in some patients, with increased distress apart from its many beneficial effects.

The main reasons for these different results may be owing to differences in intervention content between studies (Table 1). First, type of exercise ranged from walking to more comprehensive programs, such as aerobics, resistance, endurance activities, strength training, hydrotherapy, balance, and flexibility training.[19] It seems that comprehensive, regular, and long-term exercise is more effective to reduce NPs and caregiver burden.[35,39] Second, frequency and duration of exercise varies from a daily program of exercise to 30 minutes 3 times a week and 30 to 45 minutes once a week, but in general, higher frequency of exercise is related to lower NPs.[19] Third, the setting in which the study was conducted can further affect our results because the nature of the patients significantly changed among nursing home, hospital, and their home.[19,29] However, there is no evidence which place of exersice is more suitable for patients with AD. Therefore, the features of optimal exercise to improve NPs are not clear.

On the other hand, another handicap about this topic is that most of the studies have tried to show how physical activity affects depression and sleep disturbances, but there is a limited research to assess the other NPs such as disinhibition, apathy, hallucinations, and anxiety. Therefore, further studies are needed to focus on relationship between physical activity and each of NPs.

## 4 | POTENTIAL MECHANISMS OF PHYSICAL ACTIVITY ON NPS

### 4.1 | Neuropathologic mechanisms

There are multiple etiologies, such as genetic (receptor polymorphism), neurobiological (neurochemical and neuropathology), psychological (eg, premorbid personality and response to stress), and social aspects (eg, environmental change and caregiver factors) for the occurence of NPs.[40,41] It is known that it is a complex process, and it is difficult to explain it for 1 reason only. Little is known about the neurobiology of NPs. Studies have indicated that different genetic factors may be associated with various NPs.[42-44] The relationship among serotonergic system genes or polymorphisms in dopamine receptors and psychotic symptoms,[42,43] polymorphic variation at the tryptophan gene and aggression,[44] and polymorphisms of serotonin gene or the interleukin-1 gene promoter and depression[45] were found in patients with AD. Neurotransmitter changes in dementia may cause NPs. It was reported that in patients with AD with aggressive behavior, ratios of choline acetyltransferase activity to dopamine D1 receptor binding and dopamine concentration in the temporal cortex were reduced[46] and that aggression and agitation may be caused by increased dopamine system activity and altered serotonergic modulation of dopamine neurotransmission.[47] In addition, lower norepinephrine levels are associated with higher depressive symptoms in patients with AD, whereas higher norepinephrine levels have been found in the substantia nigra of patients with psychosis.[48] According to some researchers, the increased concentrations of somatostatin, vasopressin, neuropeptide Y, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation may lead to lose the inhibitory effect of the hypothalamus in patients with dementia and cause stress-related symptoms, such as agitation, sleep disturbance, and restlessness.[10,49] Similar to Cushing's patients, chronic stressors and long-term elevation of stress hormones are associated with an accelereted cognitive impairment and also with depression and anxiety in patients with AD.[50,51] Another mechanism of the occurrence of NPs may be that the release of pro-inflammatory cytokines, including interleukin IL-1, IL-6, and tumor necrosis factor-α, and oxidative stress contribute to the pathogenesis of both to neuroinflammation and behavioral symptoms.[52] Last, in recent years, several studies showed that some of the NPs are associated with hypoperfusion in specific brain regions.[53,54] For example, hypoperfusion in frontosubcortical structures, temporal cortex, frontal cortex, and right middle frontal gyrus may trigger apathy, aggression, depression, and sleep loss, respectively.[53,54]

Given the well-known adverse effects of drugs to control NPs, nonpharmacological interventions have gained increasing attention in recent years. Although there is currently contradictory results of the

studies to show the impact of physical activity on NPs, it could be explained by several hypotheses through aforementioned mechanisms.[55] First, many experimental studies demonstrated that exercise can modulate the production of neurotransmitters (including dopamine, norepinephrine, and serotonin) and which, in turn, may decrease aggressive or depressive behavior.[55,56] For example, voluntary wheel-running activity increases norepinephrine in several brain regions, such as hippocampus, locus coeruleus, and amygdala, which play a role in NPs.[57] Because AD is related to serotonergic deficit that account for NPs in this disease, selective serotonin reuptake inhibitors have been used to treat agitation, depression, anxiety, aggressive behavior, and irritability successfully.[10,58,59] Similar to selective serotonin reuptake inhibitors, physical activity can also lead to raise in tryptophan and is a precursor of serotonin, resulting in an increased serotonin in the brain. Thus, it can avoid disruption of serotoninergic signaling and may have antidepression-like effect on NPs.[60,61] Both norepinephrine and serotonin stimulation are 2 important factors in enhanced brain-derived neurotrophic factor (BDNF) transcription following physical exercise.[57] It is well known that BDNF is a fundamental mediator to regulate neuronal survival, synaptic plasticitya, and neurogenesis in the brain, in particular in the hippocampus, which is the cerebral area mainly involved on memory and behavior.[57,62,63] Many studies prove that exercise can increase increased BDNF mRNA levels and other growth factors in the hippocampus and improve mental performance in experimental animals.[57,62-64] Therefore, when all these findings are considered, it can be thought that norepinephrine and/or serotonin may participate in the up-regulation of BDNF in response to exercise, and, which, in turn, they can reduce NPs in patients with AD. In addition, calcium levels in the brain are increased, which simulates dopamin synthesis during physical exercise.[65] In patients with AD, the reduced dopaminergic functions have been reported to pave the way to psychiatric symptoms (like apathy and depression) due to the deterioration of memory, motivational process, and sleep-wake regulation.[66] Therefore, dopaminergic pathways have been targeted in treatment, eg, using methylphenidate, with the resultant reduction in apathy symptoms, and improvement in global cognition, but adverse events, including delusions, agitation, anger, irritability, and insomnia in patients with AD.[67] On the other hand, patients with AD with aggression or agitation are treated by dopamine-blocking agents, such as antipsychotics, whose use in geriatric patients may be likely to increase risk of mortality as a result of cardiovascular or infectious events.[68] The regulation of levels of dopamine in the brain following physical exercise may ameliorate NPs without any serious adverse effects like drugs affecting on dopaminergic pathways. Second, it is possible that physical activity has many beneficial effects on the neuroendocrine stress system providing proper behavior. The previous experimental studies showed that long-term voluntary exercise, but not short time or long-term forced exercise, may impact HPA axis regulation, contributing to a reversal of the effects of uncontrolled stress, and providing appropriate cortisol responses to stress,[51] which, in turn, may prevent cognitive decline and NPs. Third, physical activity may provide neuroprotection against reducing oxidative stress and inflammation. Although exercise can lead to short-term inflammatory response and production reactive oxygen species, moderate-regular exercise causes more sustained antiinflammatory effect and the resistance to oxidative stress by enhancing the antioxidant defense mechanisms.[60] For example, Reuben et al found that higher physical activity was assosiated with lower levels of the inflammatory markers IL-6 and CRP in 870 adults aged 70 to 79.[69] Additionally, regular exercise has protective effect on accumulation of visceral fat, which is a source for inflammatory cytokines.[70] Moreover, because inflammation and oxidative stress are also linked to frailty, which is a significant cause of cognitive and physical disability in older adults, physical exercise may play a key role in maintaining functionality in patients with dementia in long-term indirectly.[71,72] Therefore, physical activity can be a good option for improvement in NPs by reducing oxidative stress and inflammation with limited side effects and many proven health benefits. Last, it was demonstrated that moderate-intensity exercise resulted in both acute augmentation of blood flow to the brain and higher resting cerebral blood flow and brain metabolism by means of glucose uptake in the exercise group than sedentary adults.[73,74] This effect may contribute to improve the some of NPs resulting from hypoperfusion or hypometabolism.

## 4.2 | Cognitive enhancer effects

Although NPs can occur during any stage of AD, a recent study found that there was an association of higher Neuropsychiatric Inventory scores with severity and duration of the late onset AD rather than early onset AD.[75] Therefore, any intervention, which can enhance cognitive function, may also add to reduce NPs. Recent epidemiological studies demonstrated that lifestyle changes, such as physical exercise, may delay the onset or progression of AD.[57] These studies also reported that patients with AD were less active in midlife and that inactivity (defined as not meeting physical activity guidelines) was associated with a 250% increased risk of developing AD and that high activity could contribute toa 60% decrease in the incidence of AD.[76,77]

For instance, Donovan et al found that higher amyloid-beta burden (position emission tomography measures of cortical aggregate amyloid beta) was related to increased anxious-depressive symptoms, even in cognitively healthy older people.[78] Another study showed that amyloid deposition strongly correlated with agitation in patients with AD and MCI.[79] Experimental studies with AD demonstrated that physical exercise can decrease significantly amyloid-$\beta_{42}$ protein in animal brains.[80,81] Similarly, human studies indicated that low exercisers had higher mean levels of brain amyloid than high exercisers in autosomal dominant AD mutation carriers and that high-intensity aerobic exercise decreases plasma concentrations of $A\beta_{42}$ in patients with MCI.[82]

Additionaly, although there are few exercise training and brain volumes studies, there is strong evidence that regular physical exercise can increase plasticity, synaptogenesis, neurogenesis, and volume in several brain regions, including hippocampus, medial temporal lobe, and fronto-parietal regions, which are involved in clinical conditions such as depression, anxiety, agitation, aggression, and disinhibition, respectively.[10,83-85] Similar to BDNF, insulin-like growth factor-1 and vascular endothelial growth factor, which are 2 important factors to modulate neuronal plasticity, especially in the hippocampus, are induced by exercise.[86] Addition to neuroprotection effect, it was also shown that elevated serum insulin-like growth factor-1 levels can

improve mood factors, such as depression, anxiety, anger, fatigue, and confusion.[87]

All aforementioned mechanisms indirectly support that physical exercise can ameliorate NPs by protecting neuronal integrity and enhancing cognitive functions.

### 4.3 | Cardiovascular and general well-being

All of the cardiovascular factors lead to cerebral small vessel diseases, including WMD and subcortical lacunar infarcts (lacunes), and to deteriorated brain network; thus, patients with AD may develop NPs.[88] The pevious studies domonstrated that WMD and lacunes in the right basal ganglia were associated with depression,[89,90] that psychotic symptoms were associated with lacunes in the left basal ganglia,[90,91] and that anxiety and aberrant motor behaviours were related to white matter disease.[92]

Benefits of physical exercise are well known in both the cardiovascular system and psychological health. The effects of physical exercise on metabolite processes are a decrease in serum levels of glucose, cholesterol, cortisol and metabolic syndrome, an increase in high density lipoprotein, and insulin production.[93] Physical activity can reduce endothelial dysfunction by improvement through the activation of nitric oxide/endothelial NO synthase, resulting in the arranging of angiogenesis in the brain and the maintenance of neuronal plasticity,[94] which may reduce the effect of WMD burden.[95] Increased cardiorespiratory fitness was also associated with lower WMD.[96] Therefore, physical exercise would also be helpful for NPs due to cardiovascular health.

Furthermore, besides the potential benefits for the cardiovascular system and brain, physical exercise has been shown to be beneficial for fatigue, sleep disorders, pain, and constipation in older adults, very common conditions in patients with AD, exacerbating NPs.[97,98]

### 4.4 | Caregiver factors

Caregiver burden increases with the progression of cognitive symptoms and the severity of NPs of the patients, and it can cause depression and other severe illnesses in caregivers.[99] Caregiver burden worsens relationship between caregiver and patients with AD, which may increase the frequency and severity of NPs.[100] Therefore, there is a bidirectional relationship between caregiver burden and NPs in patients with AD and strategies to support caregivers of patients with AD should have multicomponent interventions to improve the health and well-being of dementia caregivers. Physical exercise for people affected by AD can reduce both caregiver burden and NPs, particularly in early stages of AD. It was reported that when aerobic and functional balance exercises were performed to patients with AD over 6 months for 60 minutes 3 times per week, caregiver's burden significantly decreased compared with controls.[38] Moreover, walking with relatives and regular long walking time can relieve sundown syndrome and improve sleep quality, which are major factors of caregiver burden.[30] On the other hand, balance-gait impairments, falls, or fear of falling, which are more frequent in older patients with dementia, may result in a decline in daily living activities, which leads to decreased functional ability and a loss of independence.[98] Because it is well known that more funtional dependence is associated with more caregiver burden, physical exercise can contribute to maintenance motor and nonmotor functioning of the patients with AD by increasing muscle mass, endurance, and muscle strengthening; thus, it can lead to a reduced caregiver burden indirectly.[98] Accordingly, a caregiver who is less distressed by NPs is more likely to exhibit more positive behaviors toward the patient, which may contribute to further alleviation of NPs.[10]

Patients with AD should try to engage in physical activity through all stages of the condition. When possible, they should aim to meet the recommended physical activity guideline of at least 150 minutes of moderate-intensity aerobic physical activity throughout the week.[101] However, it should be noted that this will not be achievable in the later stages of the condition. To engage patients with AD in programs of physical activity, specific barriers will need to be considered, and these are dependent on the stages of AD and the individual. Those individuals with early stages of dementia should still be predominantly independent and could acquire recommended levels of physical activity through a number of activity domains (structure exercise/sport, active travel [walking/cycling], household activity, and occupational activity). Those in the later stages of AD will likely be experiencing memory loss, problems with communication and daily activities, and changes in behavior and physical problems. It would be recommended that individuals in the later stages of the condition are referred to an exercise specialist or a physiotherapist who can prescribe physical activity on an individual basis. Some appropriate activities for those in the middle stages of dementia may include Tai Chi, chair-based exercises, swimming, or walking. Activities in the later stages of AD will likely be limited and may include activities such as balancing in a standing position, sitting unsupported, or simply moving on a regular basis.

## 5 | CONCLUSION

Although there are not univocal results for showing the impact of physical activity on NPs, most of them demonstrate a positive effect of physical activity on ameliorating depression and sleep disturbances (REM sleep behavior disorder), which are common in patients with AD. The potential beneficial effects of physical activity in AD could be explained by several mechanisms including modulated production of neurotransmitters, increasing neurotrophins, reducing oxidative stress and inflammation, elevation of cerebral blood flow, HPA regulation, and supporting neurogenesis and synaptogenesis. Physical activity can also improve cardiovascular factors and general well-being and can finally reduce caregiver burden. Therefore, because of the complications associated with the pharmacological treatment, physical exercise can be considered as “potential” add-on treatment to drugs to reduce or prevent NP onset and recurrence, with no serious side effects and many proven health benefits. However, there are methodological differences of performing exercise in the literature, and the features of optimal exercise to prevent NPs are not clear. Therefore, future studies need to focus on explaining the positive effects of physical activity on each of NPs separately and identifying potential mechanisms.

## CONFLICT OF INTEREST

None declared.

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