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# Non-pharmacologic Therapies: A Different Approach to AD

Non-pharmacologic therapies, such as cognitive-based, psychosocial, movement or sensorial therapies, have been suggested to help prevent or manage Alzheimer's disease (AD). Though the rationale for the efficacy of this type of approach to AD is still being questioned, numerous randomized clinical trials are underway to determine if there is any benefit to patients with AD using these therapeutic approaches.

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**A**lzheimer's disease (AD) and other forms of neurodegenerative dementia are of growing concern in the medical field due to their increased prevalence in the elderly. The pharmacological interventions currently available have limited ability to improve dementia symptoms (cognition, function, behavioral) and quality of life (QoL).

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Therefore, there has been a growing interest in non-pharmacologic approaches, alone or in combination, with pharmacotherapy. Several therapies have been suggested to help prevent or manage AD, and those discussed in this article include:

- cognitive-based therapies;
- psychosocial therapies;
- movement therapy; and
- sensorial therapy.

These therapies may be implemented in a variety of settings, ranging from the patient's own home to institutions, as well as individually or in a group setting. However, the rationale for their use and efficacy is still an issue. Thus, this paper presents a brief evidence-based review of the efficacy of non-pharmacologic interventions in dementia prevention and management in cognitively impaired and healthy older adults.

## **Cognitive-based Interventions**

Cognitive interventions rely on the plasticity hypothesis, which theorizes the brain may be able to achieve new or regain lost functions by transforming its constituent elements and/or internal connectivity network

according to environmental constraints.<sup>1</sup> Given this hypothesis, a certain number of environmental interventions, including cognitive interventions, could have an effect on the brain of a patient with AD.

The most frequently proposed non-pharmacologic strategies to implement during the early stages of dementia are cognitive training —“retraining” or “remediation”— and cognitive rehabilitation. Cognitive training and rehabilitation should be distinguished from cognitive stimulation and reality orientation (which involves the engagement of patients with AD in a range of activities and discussions that are typically conducted in groups). These non-pharmacologic approaches to dementia are based on the execution of various cognitive exercises, but it can be difficult to classify interventions in these categories due to a lack of clear reporting.

**Cognitive training.** The aim of cognitive training is to improve memory and cognitive functioning. Considered as a set of standardized tasks, cognitive functions include verbal memory, verbal fluency, atten-

Table 1

## Recent RCTs in Cognitive Training in Healthy Older Adults

Author	Population	Type of CST	Frequency/Length	Results
Mahncke, 2006 <sup>16</sup>	Community-dwelling U.S. adults > 60 years of age (n = 182)	Experimental computer-based training (ET) vs. Active computer-based control (AC) vs. No contact control	60 min/day, 5 days/wk for 8-10 wks	<ul style="list-style-type: none"> <li>Significant improvements in assessments directly related to the training tasks and significant generalization of improvements non-related standardized neuropsychological measures of memory (effect size of 0.25) were documented in the group using the training program</li> <li>Memory enhancement sustained after a 3-month no-contact follow-up period</li> </ul>
Valentijn, 2005 <sup>17</sup>	Community-dwelling adults > 55 years of age with subjective memory complaints (n = 139)	Collective memory training vs. Individual memory training vs. Control group	Weekly 2-hr sessions for 8 wks	<ul style="list-style-type: none"> <li>Collective training group reported more stability in memory functioning, fewer feelings of anxiety and stress regarding memory functioning, and objective memory improvement</li> <li>Improved recall of a previously learned word list in the collective training group</li> <li>Fewer feelings of anxiety and stress in relation to memory functioning in individual training group</li> </ul>
Willis, 2006 <sup>18</sup>	Older adults recruited from senior housing, community centers and hospitals/clinics from 6 U.S. cities (n = 2,832)	Memory training vs. Reasoning training vs. Speed of processing training vs. Control group	6 wk intervention (10 sessions) followed by a 4 session booster training at 11 and 35 months	<ul style="list-style-type: none"> <li>Cognitive training improved the specific targeted cognitive trained abilities (self-reported) with a sustained benefit of 5 years</li> <li>Only reasoning training resulted in less functional decline in self-reported instrumental ADLs</li> </ul>

tion, comprehension, language and executive functions. The training of these tasks can be implemented in various settings or formats, such as individual or group sessions, pencil-and-paper or computer-based exercises. The training sessions can vary in frequency, duration, difficulty levels and scope (some interventions are very specific, while others are more multimodal) depending on the subjects' level of ability.<sup>2</sup>

**Cognitive rehabilitation** is a more complex approach, defined as the use of "any intervention strategy intended

to enable patients, and their families, to live with, manage, bypass, reduce or come to terms with deficits precipitated by injury to the brain."<sup>3</sup> It is an individualized therapeutic approach which relies on the identification of individual needs and goals, developing the best strategies to compensate for the patient's impairment. The goal of cognitive rehabilitation is to enhance performance in everyday life and improve functioning in the everyday context, rather than on cognitive tests or tasks, and to capitalize on intact domains to help maintain cog-

niton and prevent or delay decline.<sup>2</sup>

A 2007 Cochrane review examined the efficacy of cognitive rehabilitation/training in patients with early stage AD and/or vascular dementia in five domains from nine RCTs—participant scores on cognitive screening measures, neuropsychological tests, self-reported functioning, informant reports on participant functioning and reactions to memory and behavior. Despite some positive results observed in certain cognitive domains, there were no significant differences between cognitive train-

ing and control groups in any of the studied domains.<sup>4-13</sup> However, the authors suggested that some gains brought about by this type of intervention may not be captured adequately by the outcomes chosen for the trials (*i.e.*, use of neuropsychological tests rather than specific effects on target skills) or due to the absence of standardized outcomes. No conclusions could be drawn about the efficacy of cognitive rehabilitation interventions due to the lack of randomized control trials (RCTs), and no significant negative effect was noted, despite previous suggestion of deleterious effects on mood.<sup>14</sup>

Since this review, a study by Bottino et al examining the efficacy of cognitive rehabilitation combined with caregiver support and use of cholinesterase inhibitors (ChEIs; *e.g.*, rivastigmine and donepezil) in patients with mild AD reported a significant improvement in Mini-mental State Examination (MMSE) scores and backward digit span scores in favor of the intervention group.<sup>15</sup>

No significant benefits have been demonstrated from cognitive interventions in dementia. This result should be taken with caution given the low level of available evidence.

Three recent RCTs considered the effects of cognitive training on cognitive function in the elderly (Table 1).<sup>16-18</sup> These three trials found cognitive training to have a beneficial effect on cognition, especially in the cognitive domains directly related to the intervention.<sup>16-18</sup> Further, a recent meta-analysis of RCTs reviewed the evidence for the effects of discrete cognitive exercise training regimen on longitudinal (> three months) post-

training neuropsychological performance in healthy older adults.<sup>19</sup> The meta-analysis of the seven RCTs included revealed positive results, with a strong effect size for cognitive exercise interventions compared with wait-and-see control conditions. RCTs with extended follow-up (> two years) did not produce lower effect size estimates than others. However, the results of these tests are difficult to extrapolate to everyday function or dementia prevention.

The evidence for cognitive exercise training in healthy older adults suggests persistent protective effects on longitudinal cognitive performance. This type of intervention appears promising so far, but needs to be confirmed in further research. The application of these benefits in everyday life situations should be better studied.

**Cognitive stimulation.** In this therapy, patients engage in a range of activities and discussions (usually in a group setting) to enhance cognitive and social functioning.<sup>2</sup> This approach is based on the hypothesis that a lack of cognitive activity accelerates cognitive decline in normal aging adults and patients with dementia.<sup>20,21</sup>

**Reality orientation** is a type of cognitive stimulation<sup>22</sup> developed in the late 1950s in the U.S. to improve the QoL of confused elderly people. Basic orientation information related to time, place and persons is offered to the patient using various materials (*i.e.*, calendars, word-letter games, puzzles), mostly during collective sessions. A board presenting, for example, the name and location of the unit, the day, date, weather and current events can be created. This

therapy is based on the idea that orientation impairment hinders a patient's functioning. By providing a better understanding of the patient's surroundings, their sense of control and self-esteem can be improved during specific sessions or in a continuous manner all day long. This particular approach has been criticized, however, due to the belief that its implementation is too mechanical, lacking a sensitive or respectful manner, and may have a possible negative impact on the patient's well-being, outweighing any small cognitive improvements.<sup>23,24</sup> Moreover, the clinical significance of the improvements observed is debatable: the patient with dementia might now know what day of the week it is, but would this have any meaningful impact on this patient's life? Is time orientation sufficiently efficient in demented patients to justify such effort? Patients with dementia suffer from limitations in basic activities of daily living (ADLs), which are more relevant than disorientation. Such criticisms have led the American Psychiatric Association (APA) to draft recommendations, cautioning healthcare providers about the use of this type of therapy.<sup>25</sup>

No Cochrane review has assessed the efficacy of cognitive stimulation therapy, but the authors of a now withdrawn Cochrane meta-analysis<sup>26</sup> concluded that there were significant effects in favor of reality orientation therapy in cognitive and behavioral outcomes; the sustained benefits of this strategy remain unknown.<sup>20,27-31</sup> Also, the authors raised a number of methodological limitations, including the heterogeneity of the interventions

Table 2

## Recent RCTs in Cognitive Stimulation Therapy in Dementia

Author	Population	Type of CST	Frequency/Length	Results
Onder, 2005 <sup>32</sup>	Donepezil-treated AD patients (MMSE 14-27) (n = 156)	Home-based reality orientation program administered by the caregiver vs. No treatment	30-min sessions 3 days/wk for 25 wks	<ul style="list-style-type: none"> <li>• Significant improvements on the MMSE scale, ADAS-Cog</li> <li>• No effect on behavior</li> </ul>
Spector, 2003 <sup>33,34</sup>	Demented patients (n = 201)	Reality orientation and cognitive stimulation vs. Control group	2-weekly, 45-min sessions for 7 wks	<ul style="list-style-type: none"> <li>• Significant improvements on the MMSE scale, ADAS-Cog and QoL-AD</li> <li>• No effect on behavior</li> <li>• Cost-effective (<i>i.e.</i>, cost did not differ between groups)</li> </ul>
Tarraga, 2005 <sup>35</sup>	Mild AD subjects treated with ChEIs (n = 46)	Interactive multimedia internet-based system associated with integrated psychostimulation program (8 hrs/day) and ChEIs vs. Interactive multimedia internet-based system and ChEIs vs. ChEIs	Internet-based system: 3 weekly, 20-min sessions for 24 wks  Integrated psychostimulation program: 8 hrs/day for 24 wks	<ul style="list-style-type: none"> <li>• Greater improvement on ADAS-Cog and MMSE with multimedia internet-based system associated with integrated psychostimulation or integrated psychostimulation program alone, as compared to ChEIs alone</li> </ul>

proposed in the different studies. Since the publication of this review, other trials have been published, and their results are listed in Table 2.<sup>32-35</sup>

There is some limited evidence in favor of reality orientation therapy in dementia, but further research is required to define the optimal modalities and the long-term effect of this strategy.

### Psychosocial Therapy

Psychosocial therapy is an intervention that is intended to enhance self-esteem, well-being and social or communication skills, and to stimulate residual memory skills or decrease behavioral disturbances.

**Reminiscence therapy** is one of the most popular psychosocial inter-

ventions in dementia care. Introduced in the 1980s, this approach is based on evocation and discussion with another person or group of people known to the patient about past activities, events and experiences, and usually using a variety of supports (*e.g.*, photos, past personal familiar belongings, music and archive sound). Contrary to individual therapy carried out in one-to-one settings, it is usually performed during general reminiscence group sessions involving several patients, but individualized reminiscence approaches also exist. The patients' families and relatives are invited to attend the sessions, with caregivers often actively involved in the preparation of a session by choosing the memo-

ries and associated material. The content and goals (related to patient or caregiver) vary. As the recall of some memories can be traumatic or stressful, potential deleterious effects should be carefully assessed.

Very few RCTs have assessed reminiscence strategies in dementia. A Cochrane meta-analysis performed in 2005 among five small RCTs or quasi-randomized studies concluded that reminiscence therapy presented significant improvements in cognition and depressive symptoms as compared to "no treatment" and "social contact" control conditions (limited to biographic memory).<sup>27,36-40</sup> The effect was sustained for four to six weeks after cessation of the intervention. Behavioral func-

tion was improved at the end of the intervention period. No harmful effects were identified on the outcome measures reported. Only one trial compared reminiscence therapy with a social contact comparison group, and found no significant differences for behavioral, communication and well-being outcomes, but showed a beneficial effect of reminiscence therapy on cognition.<sup>38</sup>

Several trials have been conducted since this review, but there is still an urgent need for more well-designed trials with robust conclusions. Haslam et al compared group reminiscence and individual reminiscence activities vs. a group control activity, and concluded that there were significant improvements in cognitive and well-being in the reminiscence group only.<sup>41</sup> However, in a methodologically sound study by Ito et al, the authors did not find any significant improvement in primary outcomes (*i.e.*, cognitive function and behavioral activities) in the studied reminiscence therapy group where patients had been diagnosed with vascular dementia.<sup>42</sup>

In their study, Wang et al assessed group reminiscence therapy (eight weekly sessions) in cognitively impaired elderly people on the progression of cognitive impairment (MMSE); mood (Geriatric Depression Scale short form [GDS-SF]); and the Cornell Scale for Depression in Dementia (CSDD).<sup>43</sup> The authors reported a significant improvement in cognitive function and affective function as measured by MMSE and CSDD.

There is, however, little evidence for the use of reminiscence therapy. The number of trials remains very

low and their quality is often poor. Further, if they are performed, any deleterious effects should also be better reported.

We are still waiting for the results of ongoing trials, including trials of a multi-centre, pragmatic RCT performed by Woods et al assessing joint reminiscence groups for people with dementia and their family caregivers on QoL and caregivers' mental health (General Health Questionnaire-28 [GHQ-28]).<sup>44</sup>

**Validation therapy.** Communication issues are particularly inconvenient and usually increase as dementia progresses. Validation therapy was developed by Feil in the 1970s to treat patients with cognitive impairments, and then was used for dementia;<sup>45</sup> this therapy can be used regardless of dementia severity. The aims of this therapy are to promote communication with the demented subject and stimulate remaining communication skills. This approach can only be offered by trained staff as it relies on the identification and comprehension of the patient' feelings, and their acceptance and validation by verbal and non-verbal communication tools.<sup>46</sup> Of note, validation therapy theory and techniques have been criticized.<sup>47</sup>

A 2005 Cochrane review assessed validation therapy in dementia,<sup>48</sup> but could not perform a meta-analysis due to the large heterogeneity observed between the included RCTs.<sup>49-51</sup> No difference was observed on cognitive or functional decline in any of the 3 included trials. One trial<sup>49</sup> demonstrated significant improvements in behavior as compared to usual care, and another in

depression vs. social contact.<sup>51</sup> These results had a limited level of evidence, and the authors concluded that the benefits observed "might simply reflect changes resulting from any structured group activity or from extra attention given to individuals."

Since this review, no other methodologically sound large-scale RCT of validation therapy has been conducted. Two trials have assessed the effects of emotion-oriented care, a combination of reminiscence and validation therapy. One failed to provide evidence for significant efficacy on behavioral outcomes.<sup>52</sup> The second demonstrated an improvement in emotional balance (less anxiety) and self-image (less dissatisfaction) in mild-to-moderate AD residents in nursing homes, as compared to usual care.<sup>53</sup>

The very limited information from RCTs is insufficient to draw any reliable conclusion about the efficacy of validation therapy in dementia. Further research should aim to address this issue.

### Sensory Therapy

Various sensory therapies have been developed in dementia, including aromatherapy, music therapy, light therapy and Snoezelen therapy. They are discussed below.

**Aromatherapy** is defined as the use of pure essential oils from fragrant plants and can be presented in various forms (oil burners, bath water, massage). Due to its perceived safety profile, great interest has been placed on aromatherapy. Based on this therapy's supposed properties of relaxation and pain relief, the application of this therapy in demented

subjects with impaired language function, confusion and limited verbal interaction capabilities could be interesting, and help improve QoL or reduce behavioral and psychological symptoms of dementia (BPSD). It is claimed to reduce behavior disturbances, promote sleep, and stimulate motivational behavior.

A 2008 Cochrane review investigated the efficacy of aromatherapy in cognition, function, behavior, QoL and relaxation in patients with dementia among four RCTs.<sup>54-58</sup> Again, a meta-analysis was not possible (inadequate data format) and the only trial<sup>55</sup> allowing analysis showed a significant treatment effect in favor of a

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four-week aromatherapy intervention on agitation and neuropsychiatric symptoms. The results should be taken with caution given the methodological limitations of the trial (*i.e.*, concomitant psychotropics and changes in prescription were allowed). Other trials reported conflicting results, but a cross-over trial<sup>56</sup> showed a beneficial effect of lavender oil vs. odorless sunflower oil on agitation (however this design is not the most appropriate in chronic disease), while another found no significant benefit.<sup>58</sup>

Aromatherapy has many methods of delivery/application. When applied through massage, the role of aromatherapy itself should be distinguished from the role of massage. This point is particularly important

since massage might be beneficial in agitation, as has been shown by a Cochrane review assessing regular massage, therapies focused on finger pressure and therapeutic touch.<sup>59-61</sup> Theoretical models to explain the benefits of massage include the reassuring influence of massage as a way to “stay in touch” when verbal communication is altered.

Despite the results of the recent studies noted above, there is still insufficient data to enable conclusions to be drawn about the efficacy of aromatherapy in the treatment of patients with dementia; further investigations are needed. A large variety of essential oils and combinations are

available and should be better explored and compared, as well as the modes and frequency of delivery, dosage and duration.

**Music therapy** is defined as the use of music and/or musical elements (*i.e.*, voice, sound, rhythm) by a qualified music therapist, as part of activity sessions or at certain times of day (*e.g.*, meal times, bath time). This non-pharmacologic approach is believed to promote non-verbal communication, relationships, learning, expression and any other relevant objectives allowing the satisfaction of physical, emotional, social or cognitive needs. The goals of this therapy are to:

- stimulate abilities and social interactions;
- cope with emotional problems;

- increase QoL; and/or
- decrease behavioral disturbances, especially when language is no longer possible.

Music therapy can be delivered on an individual or group basis, and may be active or receptive, depending on whether or not the subjects are involved in the music creation.

A Cochrane review published in 2006 assessed the effect of a minimum of five sessions of music therapy in the treatment of behavioral, social, cognitive and emotional problems in dementia.<sup>62-68</sup> However, a large number of limitations were noted, and a meta-analysis could not be conducted among the five RCTs due to the poor-quality reporting and frequently inadequate data analysis (baseline measure and correlated measures not taken into account).<sup>63-68</sup>

Several RCTs have been conducted since this Cochrane review. Raglio et al assessed music therapy vs. education support or entertainment activities on BPSD, and found a significant decrease in the Neuropsychiatric Inventory (NPI) score in the experimental group until four weeks after intervention cessation.<sup>69</sup> A cross-over RCT by Holmes et al reported a beneficial effect on apathy in AD patients, with greater engagement during live music therapy as compared to pre-recorded music therapy or silent sessions.<sup>70</sup> More recently, Guetin et al assessed the effects of music therapy compared to control sessions on anxiety and depression among mild-to-moderate AD patients in nursing homes.<sup>71</sup> Significant improvements were noted in anxiety and depression for up to eight weeks after the discontinuation of music therapy.

The quality of music therapy RCTs has been poor. There is insufficient evidence for any useful and firm conclusion of potential benefit of music therapy, given the methodological limitations of the currently available studies. Further well-conducted trials are required. One future cross-over trial will assess the efficacy of music therapy (Thai traditional music) in 60 demented subjects on depression, ADL, behavior and sleep quality over four weeks after a one-month intervention.

**Light therapy** was initially developed for mood disorders, and circadian disturbances. It has been suggested that, in dementia, daytime somnolence, nocturnal wakefulness or agitation could be brought about by degenerative changes to the circadian rhythm and could be susceptible to improvement through light therapy. Light therapy consists of daily light exposure near the visual field, miming bright natural light. The intensities and duration of light therapy are not clearly defined but usually range from two to 10,000 lux during 30 to 120 minutes.

A 2009 Cochrane review assessed the evidence for light therapy in managing cognitive, sleep, functional, behavioral, or psychiatric disturbances associated with dementia.<sup>72</sup> Eight trials were included. The interventions studied vary in terms of:

- amount of exposure (*e.g.*, the Brite Light Box®, requiring patients to sit in front of the box, vs. less invasive and demanding exposures through diffusers, at a distance from the patient);
- session duration and frequency;
- time of the session (morning,

afternoon, evening); and

- overall treatment duration.<sup>73-82</sup>

Despite bright-light therapy being found to have a positive effect on functional limitations after six weeks of intervention in the highest-quality trial,<sup>82</sup> no beneficial effect was observed for any outcome in the meta-analysis, possibly due to an insufficient sample size and heterogeneity in the study populations (dementia type and severity).

Since this review, another RCT assessed the effects of bright light therapy on agitation and sleep in people with dementia. The authors reported an improvement in sleep, but could not demonstrate any reduction in agitation in people receiving active treatment.<sup>83</sup>

Despite these results, there is no strong evidence to support any value of light therapy in dementia. Further research is required to determine whether light therapy is effective and, if so, to further define the best types of exposure (*i.e.*, lux, session and intervention durations, time of day). We are still eagerly awaiting the results of a two-year study assessing bright-light therapy on depressive symptoms and sleep wake symptoms among subjects with early AD, mild cognitive impairment (MCI) and subjective memory complaints.<sup>84</sup>

**Snoezelen therapy**, or multi-sensory stimulation, was introduced in the Netherlands in the late 1970s for patients with intellectual and learning disabilities. This therapy is based on the stimulation of sight, hearing, touch, taste and smell, through the use of light, tactile surfaces, music and essential oils. It is believed to be beneficial to place

patients with reduced cognitive skills and communication abilities in less cognitively demanding environments and stimulate their residual sensorimotor abilities. Snoezelen is often used to improve behavior disturbances and mood, or to enhance communication. These patients are usually placed in a closed area, reproducing a pleasant, relaxing and safe atmosphere, with programs frequently based on two or more 30- to 60-minute sessions per week, for six to eight weeks. Various clinical applications do exist (*i.e.*, form, nature, principles and procedures); Snoezelen assessment remains complex.

A 2008 Cochrane review examined two trials which assessed the short- and long-term effects of Snoezelen therapy on behavior, mood and communication in patients with moderate-to-severe dementia, but could not be pooled.<sup>85</sup> The first trial was based on eight one-to-one 30-minute Snoezelen sessions twice a week and assessed the effect on behavior, mood and cognition in 136 demented subjects.<sup>86</sup> The second was a clustered RCT conducted among 125 demented patients in a nursing home, and assessed daily integrated Snoezelen care offered for 15 months by certified nursing assistants.<sup>87</sup> The latter trial suggested an immediate beneficial effect in maladaptive behavior, mood, and interaction, but these benefits concerned instrument subscales rather than overall performance in mood or behavior. Finally, both trials were considered of inadequate methodological quality for the review, which concluded that there were no significant short- or long-term effects on cognition, behavior,

Table 3

## Recent RCTs Assessing Physical Exercise in Dementia

Author	Population	Intervention	Frequency/Length	Results
Kemoun, 2010 <sup>104</sup>	AD subjects (MMSE < 23), able to walk 10 m without technical assistance (n = 31)	Physical activity program (walking, exercises, equilibrium, and endurance) vs. No physical activity	3-weekly 1-hr sessions for 15 wks	Significant improvement on overall Rapid Evaluation of Cognitive Functions score (ERFC French version) and on walking efficiency (walking speed and stride length)
Eggermont, 2009 <sup>105</sup>	Nursing-home residents with moderate dementia (n = 97)	Physical activity program (walking) vs. Social visits	30-min sessions, 5 days/wk, for 6 wks	No significant effects of intervention on cognitive function (memory domain, executive function domain and total cognition domain)
Steinberg, 2009 <sup>106</sup>	Patients with AD (n = 27)	Home-based exercise intervention delivered by the caregiver vs. Home safety assessment tool	N/A	<ul style="list-style-type: none"> <li>• Good adherence to the exercise program</li> <li>• Trend for improvement on hand function and lower extremity strength (primary outcomes)</li> <li>• Trend for worse depression and lower QoL ratings (secondary outcomes)</li> </ul>
Santana-Sosa, 2008 <sup>107</sup>	Patients with AD (n = 16)	Exercise training program (resistance, flexibility, joint mobility, and balance/coordination exercise) vs. Control group	12 wks	Significant improvements in upper and lower body muscle strength and flexibility, agility and dynamic balance, and endurance fitness (using the Senior Fitness test), gait and balance abilities (Tinetti scale) and in the ability to perform ADLs independently (Katz and Barthel scores)
Williams, 2008 <sup>108</sup>	Nursing-home residents with moderate-to-severe AD (n = 45)	Individualized comprehensive exercise routine sessions (strength, balance and flexibility, walking) vs. Supervised walking vs. Social conversation	30-min sessions, 5 days/wk, for 16 wks	Greater benefit in exercise group on depression (CSDD)

mood or communication/interaction.

One 12-week single-blind pilot study has since been conducted, testing the effects of Snoezelen therapy in dementia on daily observation scales or the Clinical Global

Impression Improvement (CGI-I). The authors reported a dose-effect improvement on CGI-I, which was sustained for 12 weeks after discontinuation of the sessions.<sup>88</sup>

However, the available evidence

is still insufficient to conclude as to the efficacy of Snoezelen therapy in the management of maladaptive behavior, mood, interaction and communication in dementia. Further, more rigorous RCTs are needed.

### Movement Therapy

**Physical activity** can be used in a wide variety of target populations, including healthy aging adults and patients with dementia, even in severe stages, using passive movements.

The benefits of movement therapy have been demonstrated in terms of depression,<sup>89</sup> QoL,<sup>90</sup> falls,<sup>91</sup> cardiovascular function<sup>92</sup> and disability<sup>93</sup> rates. Further, regular exercise can slow down or prevent functional decline associated with aging and improve muscle mass, arterial compliance, energy metabolism, cardiovascular fitness, muscle strength and overall functional capacity.<sup>94</sup>

Several components of physical fitness, which can be combined or alone, have been described and include cardiorespiratory and muscular fitness (muscular endurance and strength), flexibility (stretching techniques) and balance. Cardiorespiratory fitness, also called aerobic training, is a condition in which the cardiovascular and respiratory systems function together to ensure that adequate oxygen is supplied to the working muscles to produce energy. A high level of cardiorespiratory fitness permits continuous physical activity without a decline in performance and allows for rapid recovery following tiring physical activity. Also, it is believed that cardiovascular fitness can improve cognitive capacities. Animal research has suggested physiopathology for a beneficial effect of aerobic physical activity on cognition, through increased cerebral blood flow, oxygen extraction and glucose utilization<sup>95</sup> or activation of growth factors involved in capillary density.<sup>96</sup> The physiopathology of physical exercise in dementia has also

been studied in animal models, which have suggested that it may decrease the pathophysiology of dementia.<sup>97</sup> Physical activity could act as a protective factor for cognitive decline and might maintain a low cerebral blood flow, thus decreasing cardiovascular risk.<sup>98</sup>

A 2008 Cochrane review further examined the effects of physical activity (*i.e.*, aerobic exercise training or physical activity of any length) in dementia on cognition, function and behavior, as well as caregiver outcomes and use of healthcare services.<sup>99</sup> Four RCTs compared activity programs with usual care in dementia using adequate allocation concealment.<sup>100-103</sup> The programs tested ranged from 30-minute sessions three times a week during two weeks to twice-weekly one-hour sessions.<sup>102-103</sup> Only two trials were included in the meta-analysis (adequate data unavailable). Despite one trial reporting significantly slower decline in ADLs following a collective exercise program (walking, strength, balance, and flexibility training), no significant results were observed in the meta-analysis for cognition, function, behavior, depression or mortality.

Since this review, five new RCTs have been conducted and their results are listed in Table 3.<sup>104-108</sup>

Given the very limited evidence currently available, it is difficult to determine whether physical activity is beneficial for cognition, function, behavior, depression and mortality in people with dementia. Furthermore, movement therapy is prone to numerous variations concerning:

- the exercise type (*i.e.*, aerobic, walking, isotonic exercises,

muscular strength, single or multiple activities);

- intensity (low, moderate or high);
- frequency (one to six weekly sessions);
- session duration (20 to 150 minutes); or
- intervention duration (two to 112 weeks).

Physical activity might be beneficial for dementia, but further studies are required to determine the most effective interventions. More homogeneous study populations, in terms of dementia type and severity or level of mobility, should be used because they influence the feasibility of the intervention. Any potential adverse effects should also be better investigated (*e.g.*, falls, fractures). Several uncertainties also remain, including how long exercise effects last after cessation of training or how much exercise is needed to reinstate previously observed benefits.<sup>109</sup>

Few trials have investigated the benefits of physical activity among older adults with MCI. A 2005 study by Scherder et al showed an improvement in executive functions comparing a walking group, hand and face exercises, and a control group among 43 frail elderly subjects with MCI.<sup>110</sup> High-intensity aerobic exercise vs. a stretching control group suggested sex-specific effects on cognition (*i.e.*, improved performance on multiple tests of executive function for women, but beneficial effect on one test only among men)<sup>111</sup> in 33 MCI subjects.

For the prevention of cognitive decline, it is important to distinguish between aerobic and anaerobic exercise. A recent Cochrane review assessed the effects of aerobic physical

activity on cognitive function among healthy older adults.<sup>112</sup> Eleven RCTs assessing any exercise program aiming at improving cardiovascular fitness of any intensity, duration or frequency were included.<sup>113-123</sup> The cognitive domains assessed varied considerably between studies. Among the 11 RCTs, eight reported increased cardiorespiratory fitness (average 14% increase in maximum oxygen uptake test [VO<sub>2</sub> max]) using aerobic exercise interventions. Improvements in at least one domain in cognition were also observed, with the largest effects being seen in motor function (standardized effect size 1.17) and auditory attention (standardized effect size 0.50). Moderate effects were also observed in cognitive speed (standardized effect size 0.26) and visual attention (standardized effect size 0.26). A large number of cognitive domains were explored and most of them did not show significant improvement. In this context, the review pointed out the need for more homogeneous and reproducible cognitive tests to enhance future research. As a matter of fact, other meta-analyses have produced varying results,<sup>124-126</sup> which could be explained by the search period and the stringency of the inclusion criteria regarding study design, but also the results seem to crucially depend on the study population, inclusion criteria and cognitive tests.

Since this review, a 24-week physical-activity intervention trial, where 60% of patients presented with MCI, observed a significant, although modest, benefit on the ADAS-Cog scale (1.3 point difference between groups, with a mean baseline score of 7) after cessation of

the intervention, which was sustained until 18 months.<sup>127</sup>

There is evidence that aerobic physical activity improving cardiorespiratory fitness is beneficial for cognitive function in healthy older adults, especially in motor function, cognitive speed, and auditory and visual attention, although the question of which other aspects are positively affected requires further research. To date, there is insufficient evidence to affirm that improvement in cardiovascular fitness mediates improvement in cognitive function, and it is possible that improvement in cognitive domains could be explained by mechanisms other than aerobic fitness.<sup>125</sup>

Given that several potentially effective non-pharmacologic approaches have been suggested, especially in dementia prevention, it may be of use to develop multidomain interventions since these different approaches may have synergistic effects.<sup>128</sup> Due to the multifactorial nature of AD, it would seem logical to combine several strategies (*i.e.*, physical exercise, nutrition, cognitive stimulation) to examine not only the individual effects of each intervention, but also any potential synergistic effects. Several multidomain trials have been designed with this goal in mind.<sup>129-131</sup> However, multidomain trials are also prone to several specific challenges regarding blinding conditions and appropriate control group, population selection, or intervention observation.<sup>132</sup> It is also difficult to identify the independent effects of each factor, because they may act through common mechanisms (*e.g.*, via cardiovascular mechanisms) and there may be between-group contamination.

## Conclusions

Non-pharmacologic therapies have been studied in dementia prevention and management in order to try and improve cognitive, emotional and behavioral changes related to dementia, to the remaining skills of patients with dementia, and to enable them to better adapt their lifestyles to their level of functioning. Some therapies target specific symptoms/processes of dementia (*i.e.*, cognition or BPSD), while others are based on non-specific procedures. Other reviews have investigated the effectiveness of various non-pharmacologic strategies according to outcome measures, either focused on one domain, most frequently BPSD,<sup>133-135</sup> institutionalization,<sup>136</sup> or wandering,<sup>137</sup> whilst others have provided a broader comprehensive overview.<sup>138</sup>

Despite an increasing interest of several strategies, the efficacy of non-pharmacologic interventions remains poorly investigated. This could be partially explained by a lack of commercial interest in the development of non-pharmacologic rather than pharmacologic strategies and specific methodological challenges.<sup>138</sup> The available rigorous evidence concerning non-pharmacologic strategies therefore remains very limited.

A Consolidated Standards of Reporting Trials (CONSORT) extension for standard reporting in non-pharmacologic treatment is available<sup>139</sup> and should help to improve the reporting of such trials as papers focus on the challenges linked to blinding.<sup>140-141</sup>

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