THE IMPACT OF NON-PHARMACOLOGICAL TREATMENT ON SYMPTOM REDUCTION AND PROGRESSION OF MILD COGNITIVE IMPAIRMENT TO DEMENTIA

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ABSTRACT
Mild cognitive impairment, also considered a „pre-dementia“ stage, has a prevalence of 10-20% in people aged 65 or more. The risk increases with age and is higher in the male gender. Nearly 10% to 15% of MCI patients progress to a diagnosis of probable AD each year, relative to only 1% to 2% of the general elderly population. The importance of successfully treating this early illness phases cannot be overstated. At the moment there is no solid pharmacological evidence of a drug that can improve symptoms of mild cognitive impairment or delay its progress to dementia. The current treatment options include: reducing cardiovascular risk factors and prevention of stroke. Social engagement, aerobic exercise, mental activity may help reduce further cognitive decline. In this review we take a closer look at the impact of non-pharmacological treatment on symptom reduction and progression of mild cognitive impairment to dementia.

Key words: cognitive training, mild cognitive impairment, physical activity.

REZUMAT

În această analiză vom sintetiza impactul tratamentului non-farmacologic asupra reducerii simptomelor și al progresului către demență la pacienții cu tulburări cognitive ușoare.

Cuvinte cheie: antrenament cognitiv, tulburare cognitivă ușoară, activitate fizică.

MILD COGNITIVE IMPAIRMENT (MCI)
Mild cognitive impairment is situated between „normal aging process” and dementia. The Alzheimer Association and National Institute of Aging define MCI as (I) concern regarding a change in cognition from the patient, knowledgeable informant, or from a skilled clinician observing the patient, (II) objective evidence of impairment (from cognitive testing) in one or more cognitive domains, including memory, executive function, attention, language, or visuospatial skills, (III) preservation of independence in functional abilities and (IV) no evidence of a significant impairment in social or occupational functioning (1). MCI differs mainly from dementia because its preservation of independence in functional abilities and lack of significant impairment in social or occupational functioning (2).

The same organisations define MCI due to Alzheimer’s disease as memory impairment, longitudinal decline in cognitive function and lack of evidence for vascular, traumatic, or other medical causes of cognitive decline (1,2).

The DSM-5 refers to it as “mild neurocognitive

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Non-pharmacological Treatment: The Impact of fluoxetine showed some promising results as discussed and acupuncture (22). Of the ones mentioned, only compounds which enhance nerve growth factor synthesis Yamabushitake mushroom (21) – thought to have (19), combination of green tea extract and l-theanine (20), transdermal nicotine (17), melatonin (18), fluoxetine (14), acetyl-L-carnitine (15), intranasal insulin (16), anti-inflamatory agents (refecoxib) (12), peroxisome for men and conjugated equine oestrogen for women), (piribedil), sex steroid hormones (testosterone injections selegiline, Ginko Biloba), dopamine receptor agonists galantamine, donepezil), antioxidants (Vitamine E, acetylcholinesterase-inhibitors (rivastigmine, treatments for MCI.

progression it is highly important to find an early cerebral-vascular disease (11) the rate of progression to dementia varies between studies. If the person already has heterogeneity of MCI, given that the progression rate to dementia within 3 years was 3.6. This pleads to the within a 3 year period. The relative risk of progressing to dementia within 3 years is 3.6. This leads to the heterogeneity of MCI, given that the progression rate to dementia varies between studies. If the person already has a cerebral-vascular disease (11) the rate of progression to dementia is 50% in 5 years. Given the high rate of progression it is highly important to find an early treatment for MCI.

Amongst the treatments used in trying to manage MCI and/or delay progression to dementia are: acetylcholinesterase-inhibitors (rivastigmine, galantamine, donepezil), antioxidants (Vitamine E, selegiline, Ginko Biloba), dopamine receptor agonists (piribedil), sex steroid hormones (testosterone injections for men and conjugated equine oestrogen for women), antiinflammatory agents (refecoxib) (12), peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonists (rosiglitazone and pioglitazone) (13), vitamin B complex (folic acid, cyanocobalamin and pyridoxine) (14), acetyl-L-carnitine (15), intranasal insulin (16), transdermal nicotine (17), melatonin (18), fluoxetine (19), combination of green tea extract and l-theanine (20), Yamabushitake mushroom (21) – thought to have compounds which enhance nerve growth factor synthesis and acupuncture (22). Of the ones mentioned, only fluoxetine showed some promising results as discussed below. In some studies, PPAR-gamma agonists showed some improvements in patients with diabetes and MCI, but it is most likely as a part of controlling metabolic risk factors.

MEDICAL TREATMENT

Currently there is no effective drug for the treatment of MCI. Cholinesterase inhibitors have not been shown to decrease risk of progression from MCI to dementia at 1 and 3 years, they have limited to no significant effects on cognitive function over the short-term (<12 months) and may substantially increase adverse effects based on a meta-analysis of 4 trials (n=1,960) and another of 9 trials (n=5,149) (7,23). Some hypotheses for the lack of sustained benefit of cholinesterase inhibitors are: the compensatory upregulation of central cholinergic activity, lack of sensitivity of the cognitive outcomes of our current measurement tools, and heterogeneity of patients (24). Recent studies show that long-term treatment with SSRI (>4 years) in patients with MCI and previous depression was associated with a 3-year delay in progression from MCI to Alzheimer’s dementia (25) which represent a very promising result worthy for further studies.

A randomised control trial of 45 participants (26) found that lithium treatment (target serum level 0.25–0.5 mmol/l) decreases P-tau concentrations in the cerebrospinal fluid, improves cognition and has good tolerability and adherence. Lithium shows disease modifying potential (26,27) through interaction with enzymatic activity, thus reducing Tau phosphorylation and increasing synaptic plasticity.

Ginko-biloba supplements, widely used supplement in MCI patients, has not been shown in randomized control trials to prevent cognitive decline (28).

A key point in reducing the risk of progression from MCI to dementia is to control the vascular risk factors (29). That can be achieved through blood pressure control, smoking cessation, statin therapy, anti-platelet therapy, and anticoagulation or antithrombotic therapy for atrial fibrillation (30,31).

Given the lack of efficiency of the pharmacological treatment, other methods that can stop progression to dementia are essential.

NONPHARMACHOLOGICAL APPROACH

Physical activity lowers the risk of developing cardiovascular disease, diabetes mellitus, cancer (colon and breast), obesity, hypertension, bone and joint diseases and depression (32). Also, it was positively associated with general well-being, low levels of anxiety and depression and overall positive mood (33). In a study (34) of 28 adults with minor depression, running reduced depressive symptoms and it proved to be as effective as psychotherapy. In regard to anxiety (35), aerobic exercises improved symptoms more than weight training or flexibility exercises. To significantly reduce trait anxiety,
exercise programmes need to exceed 21 minutes per session for a minimum of 10 weeks (36).

The mechanisms through which physical exercise could improve cognition in patients with MCI or dementia are: increasing in blood flow and oxygen supply to the brain, lowering blood pressure, reducing inflammatory markers, improving endothelial function (37). It may also increase the volume of the hippocampus (38). It has been shown in animal studies (39) that exercise stimulates neuron proliferation in hippocampal areas.

A controlled trial (40) of 33 patients with amnestic MCI aged 55 to 85 (with a mean age of 70 years) were randomized either to a high-intensity aerobic exercise or stretching control group. Six months of high-intensity aerobic exercise (4 days/week for 45 to 60 minutes per session using either treadmill, stationary bicycle or elliptical trainer) had sex-specific effects on cognition, glucose metabolism, and hypothalamic-pituitary-adrenal axis and trophic activity despite comparable gains in cardiorespiratory fitness and body fat reduction. Their results suggest a sex bias in cognitive response may relate to sex-based differences in glucose metabolism and hypothalamic-pituitary-adrenal axis responses to aerobic exercise. The cognitive enhancement effect of aerobic exercises was better seen in executive control tasks in women together with increased insulin sensitivity and low levels of circulating cortisol and BDNF. For men, aerobic exercises increased the plasma level of insulin growth factor I and most improvements were also observed on the executive function.

A prospective study (41) of 9008 randomly selected men and women aged 65 or older explored the association between physical activity and the risk of cognitive impairment and dementia. Compared with no exercise, physical activity was associated with lower risks of cognitive impairment, Alzheimer disease and dementia of any type and high levels of physical activity were associated with increased protection of the above-mentioned diseases. However, given the study design (not randomized, placebo controlled), more evidence is needed to firmly draw a conclusion.

A control trial (42) of 100 older adults with mean age of 75 years and MCI were randomized to either a multicomponent exercise or an education group (ratio of 1:1). The exercise group worked out for 90 minutes/day, 2 days/week, 40 times for 6 months and it consisted in aerobic exercise (including stair stepping, endurance walking, and walking on balance boards), muscle strength training, postural balance retraining and dual-task training. The mean intensity of the aerobic exercise was approximately 60% of maximum heart rate. Compared with the control group, the physical exercise group showed a better MMSE and logical memories score. Patients with a low total cholesterol level before the intervention showed improvement of logical memory scores.

Another randomized control trial (43) showed modest improvement in cognition (ADAS-Cog scores) over an 18-month follow-up period (6 months of intervention with follow-up and then another follow-up 12 months after intervention ceased) in patients assigned to the physical activity group. The physical activity intervention consisted in 50 minutes sessions/day, 3 days/week for 6 months of individualized home-based program, with the most recommended activity being walking.

A RCT (44) concluded that a moderate to high intensity strength and aerobic programme did not slow the progression of dementia and may in fact worsen the cognitive decline. The exercise programme consisted of twice a week intervention for four months with each session lasting 60 to 90 minutes. In addition, the intervention arm was asked to do 150 minutes of physical activity per week at home. However, this study was done in people with dementia and the generalizability of the results are questionable.

A meta-analysis of 14 RCTs (45) revealed that 9 of the total RCTs reported improvements for at least one outcome. These were noticed in: verbal fluency, global cognition, fluid intelligence, executive function and memory. The intervention types of physical activity were mixt: moderate intensity aerobic, low intensity walking, resistance training, balance and coordination or combinations of the above. The same applied for the exercise dose and intensity: from 30-90 minutes/session, 2-4 sessions/week with durations of 6 to 52 weeks with intensities from high to low. Most interventions were provided in groups, few individual and the sites were mostly gymnasiums, home and care centres or homes. Overall results were inconsistent with benefits varying across exercise types and cognitive domains.

Another meta-analysis (46) of 30 trials reported an overall medium treatment effect for combined physical, cognitive, functional and behavioural outcomes. The mean duration of the exercise intervention was 23 weeks (with range from 2 to 112 weeks) with an average of 3.6 session/week (from 1 to 6 sessions) and each session lasting 45 minutes (ranging from 20 to 150 minutes). The main physical activity was walking combined with different isotonic exercises. This meta-analysis included patients with cognitive impairments nondemented and patients with dementia.

A meta-analysis of 15 prospective studies (47) which included non-demented patients showed that physical activity (both high level and low-to-moderate level) is a protective factor against cognitive decline. This meta-analysis lacks the specifics of the exercises used but shows no differences in results regarding intensity of physical activity.

A meta-analysis of 11 RCTs (48) concluded that aerobic exercises significantly improved global cognitive ability and weakly, but positively improved memory with no significant improvement in attention, verbal fluency or visuospatial domain. The exercises were: walking, handball training, Tai Chi, jogging, cycling, dance based aerobics and multicomponent aerobic. The sessions were 30-60 minutes/day, 2-5 days/week with a duration of 6 months to 1 year. The maximum heart rate was 60-80%
(classified as moderate activity). The improvement in global cognitive function was defined as increases in scores of MMSE/MoCA/ADAS-Cog at follow-up.

One meta-analysis of 60 RCTs (49) showed that physical exercise had a small but positive effect on improving cognition in patients with MCI and that the effect was stronger when it came to patients with dementia. This study raised the concern of the high dropout rate of patients in the active intervention group compared to control group. The duration of the intervention varied from 6 weeks to 1 year and it did not specify the type of exercises involved.

A meta-analysis of 12 prospective studies (50) concluded that a high level of physical activity can reduce the risk of cognitive decline and dementia. The assessment of physical activity was through questionnaires and exercise programmes where not described.

Physical activity could improve cognition in patients with MCI. The best results came from fitness programmes of moderate intensity (maximum heart rate between 60-80%) conducted by physiotherapists, that lasted around 45 minutes per session with 3 sessions per week for a total of about 6 months. Most improvements were found in global cognitive and executive function.

Another method of improving cognition is through cognitive training and cognitive rehabilitation programs. The concept of cognitive training and rehabilitation programs is based on enhancing neuronal plasticity, but probably different mechanisms are also in place (51). Today, cognitive programs are designed as computer softwares with an easy-to-use and accessible interface (Computerized cognitive training – CCT).

A meta-analysis of 31 RCTs (52) examined the effect of cognitive training and mental stimulation on healthy older (>50 years) adults. Compared to the control group, the cognitive intervention group showed significant improvements on the memory measures of face-name recall, immediate recall, and paired associates and on subjective measures of cognitive performance. Compared to active control group (who received educational DVDs, lectures, health-promoting training), cognitive intervention also showed significant improvements in memory measure of recognition, on the executive measures of working memory and processing speed and also on composite measures of cognitive function. Memory-based training was the most used in the cognitive intervention group. In the same meta analysis they compared the mental stimulation group (which included actions such as playing piano, acting, and helping children with reading difficulties) with control and active control groups. The mental stimulation group showed better results in fields of memory, executive function and on one measure of composite cognitive function compared to control group. Compared to the active control group there were no significant differences. It needs to be mentioned that results from the mental stimulation studies were not as strong as the ones from cognitive training due to lack of available data.

Participants with MCI showed improvements in free recall of lists of words and in memory for a persons’ name (2-month intervention with weekly 2 hour sessions) but not on text memory - in this specific study (53) it is mentioned that it might be a software bias by not designing the text memory task suitably.

In a study (54) of 127 patients whom during a 12 week period received Cognitive skills training (2 hours/week), Brain Coaching/Counselling (1 hour/week) and neurofeedback therapy (2 hours/week) showed improved on average in 4.68 (an improvement of over 3 was labelled as “high impact”) out of 10 cognitive domains. Most improvements belonged to patients who were below 60 years old and had a baseline MMSE score of minimum 28. All patients received an MRI at the beginning to exclude somatic causes and a random subset of 17 patients were also given an MRI after the completion of the trial. 9 out 17 patients shown a growth in their hippocampal volume, but it was not statistically correlated with the changes in cognitive functioning.

A RCT of 47 patients with MCI (55) found that the intervention group had a tendency to improve the effect sizes for measures of verbal learning and memory compared to control. On the other hand, the effect sizes for learning and visuospatial function tended to favour the control group (whose activities were listening to books, reading and playing the visuospatial-oriented computer game Myst). Although the results were not statistically significant it is still enough to warrant further investigation. The active intervention group did the training for 100 minutes/day, 5 days/week for 6 weeks and it consisted of exercises specifically designed to improve auditory processing speed and accuracy.

Another RCT of 27 patients (56) found an improvement on a measure of visual sustained attention in the intervention group compared to control. The active intervention group completed 30 sessions of a computerised cognitive training program. The exercises targeted the following cognitive functions: attention, processing speed, visual memory and executive functions.

A meta analysis (57) of 17 RCTs found moderate and statistically significant improvements in the active group compared to control. The improvements were seen in: global cognition, verbal learning, verbal memory, nonverbal learning, working memory (largest effect size of all cognitive domains), attention and psychosocial functioning. There were a few individual studies that reported improvements at further follow-ups after the cognitive training had ceased. The majority of studies (meaning 15 out of 17) administered supervised training. The number sessions varied from 6 to 72 with a session length between 20 and 100 minutes and a 1 to 5 sessions per week. The meta analysis mentions that the lowest risk of bias was in the studies that used the COGPACK software (which contains exercises for verbal memory, nonverbal memory, executive functions, attention and speed). There were no mentions of the effect of cognitive training on the progression of MCI to dementia.

Another meta analysis (58) of 17 RCTs concluded that cognitive intervention improves overall
cognition and has small benefits on episodic memory, semantic memory, executive functioning, visuospatial ability, attention and MMSE in patients with MCI. The interventions varied a lot from 4 weeks to 6 months of total intervention time, with 1 to 5 sessions per week, each lasting between 30 minutes and 2 hours.

Cognitive training is linked to moderate improvements in cognition in patients with MCI, best results seen in: global cognition, executive function and memory. The domains of improvement depend on the software used, with COGPAK having the lowest risk of bias. The mean session time was between 60-75 minutes, 1 to 5 sessions per week, for about 14 weeks.

In order to obtain benefits from both techniques, the researchers combine physical activity with group based cognitive stimulation training and individual cognitive stimulation training.

One study of this type (59) had 67 participants and its design consisted of 24 weeks divided into 2 phases. First phase consisted in a control period where patients did not receive any treatment, it lasted for 12 weeks and at the end of these weeks they were re-evaluated. The second phase consisted in the active intervention for 12 weeks. At the end of these weeks patients were re-evaluated. They found out that participants showed improvements in physical fitness whilst cognitive outcome measures revealed either stable performance during the control period with improvement following the intervention period (backward- digit span, letter fluency), or deterioration during the control period with stability or improvement following the intervention.

A meta analysis of 46 (21 only with cognitive training, 23 only with physical activity and 2 with both intervention) studies (60) concluded that both cognitive training and physical exercises improve executive functions with cognitive training showing a potential advantage, whereas physical exercise interventions were more consistent in results. It appears that group interventions for physical exercises produced a greater effect than individual intervention and this difference was not notable with cognitive training. This underlines the importance of social engagement as part of the programmes. Studies with the largest effect sizes from the physical exercise intervention used either fitness, strength or a combination of the two. The largest effect size for the cognitive intervention was obtained from studies with programmes containing verbal working memory exercises.

CONCLUSION
There is little evidence that physical activity and cognitive training improve cognitive function in patients with MCI but more studies with clearer methodology are needed because the current literature is of moderate quality which makes it difficult to draw a firm conclusion. It is believed that physical activity improves cognition in patients with MCI because it lowers the cardiovascular and metabolic risk factors, improves tissue oxygenation and endothelial function.

Results are mixed when it comes to slowing progression to dementia, hence more studies with longer follow-up periods are needed. To accurately measure the impact of physical exercise and cognitive training in slowing progression to dementia the follow-up must be long enough so that the control group shows clear signs of deterioration of cognitive functioning.

Unlike physical exercise programmes, cognitive training programmes are better defined, thus the more solid evidence seen in studies using the latter. There are still uncertainties regarding the effect of the two active interventions on the progression to dementia and the method through which these produce any change on cognitive functions.

Also we need to better understand the subgroups which are to benefit most of each intervention. Given the fact that this kind of interventions are virtually without side effects, are rather easy to implement and the benefits may be thorough (both mental and physical) it is to expected that this kind of treatments will largely expand in the future.

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