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Mild cognitive impairment and cognitive impairment, no dementia: Part B, therapy

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Abstract Mild cognitive impairment (MCI) and cognitive impairment, no dementia (CIND) might be the optimum stage at which to intervene with preventative therapies. This article reviews recent work on the possible treatment and presents evidence-based recommendations approved at the meeting of the Third Consensus Conference on the Diagnosis and Treatment of Dementia held in Montreal in March, 2006. A number of promising nonpharmacologic interventions have been examined. Associations exist with both cognitive and physical activity that suggest that both of these, together or separately, can delay progression to dementia. Similarly, case control studies as well as prospective long-term studies suggest a number of low toxicity interventions and supplements that might significantly impact on MCI progression; folate, B_6, and B_{12} to lower homocysteine levels, omega-fatty acids, and anti-oxidants (fruit juices or red wine) are good examples. In selected genotypes such as individuals with *APOE* e4, therapy with donepezil might slow progression. The concern, however, is that none of these therapies (including cholinesterase inhibitors) have demonstrated a clinically meaningful effect with randomized, placebo-controlled studies. Just as randomized controlled studies have failed to support primary prevention of dementia by using estrogen or nonsteroidal anti-inflammatory drugs (NSAIDs), there exists the possibility that well-designed randomized controlled trials might fail to definitively demonstrate putative or promising mild cognitive impairment interventions. Pharmacologic interventions and nonpharmacologic therapies, while tantalizing, are currently for the most part insufficiently proven to allow serious consideration by physicians. Recommendation were supported for a general "healthy lifestyle" including physical exercise, healthy nutrition, smoking cessation, and mental stimulation. Close monitoring and treatment of vascular risk factors are justified and were also supported.

Keywords: MCI; CIND; Cognitive impairment; Psychosocial intervention; Cognitive intervention; Exercise

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1. Treatment for mild cognitive impairment

The preceding article reviewed the concepts and diagnosis of mild cognitive impairment (MCI) and cognitive impairment, no dementia (CIND), reviewed our approach to an evidence-based review of the literature, and presented the recommendations that received consensus at the Third Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD3) held in Montreal in March 2006.This second part will use the same approach to review therapy for MCI and CIND. The treatment of MCI has been the subject of a number of recent chapters and reviews [1,2]. There have been relatively few randomized controlled trials of any therapy sufficient to rank as Level 1 evidence. Nevertheless, there are a number of potential interventions both pharmacologic and nonpharmacologic that deserve to be addressed.

2. Nonpharmacologic treatment for MCI

2.1. Cognitive intervention in MCI

There have been several relevant studies in this area. We will first review those carried out in normal elderly and then in MCI. A full listing of these studies is seen in Table 1. Longitudinal cohort studies of healthy elderly persons show that engagement in stimulating cognitive activities (engaged lifestyle; novel and intellectually challenging activities) is associated with better memory and verbal abilities [3]. In a case-control study, participation in intellectually stimulating and social activities in midlife has been associated with reduced risk of developing Alzheimer's disease (AD) [4]. In a longitudinal cohort study of healthy elderly persons (average follow-up, 4.5 years), a participant's frequency of participation in common cognitive activities at baseline was associated with reduced risk of clinical diagnosis of AD and reduced cognitive decline (annualized change on global cognition, working memory, and perceptual speed) during the follow-up period [5]. However, the methodology in these studies is based on association; therefore, the direction of causality remains to be clarified. For example, it is unclear whether cognitive activities have a protective effect on the development of cognitive deficits in aging, or whether reduced engagement in cognitive activities is an early sign of AD.

Verhaeghen et al [6] conducted a quantitative review of studies measuring the efficacy of memory intervention studies in healthy aging. They reported that memory training improved performance on targeted memory tasks and that the effect sizes for the training effect were in the moderate range. One large scale randomized controlled trial on cognitive interventions (memory, speed, or reasoning vs no training) was completed in a sample of 2,832 healthy older adults [7]. The results indicated improved performance after training on the cognitive domains that were targeted by the interventions. The positive effects were sustained during a 2-year follow-up, and the effect sizes were moderate to large. Thus there is good evidence that cognitive training increases cognitive efficacy on target measures in healthy older adults.

Two nonrandomized studies and two randomized controlled trials (RCTs) have been reported on the effect of cognitive training in MCI. With an RCT design, Olazaran et al [8] reported decreased depression and improved cognition (cognitive subscale of the Alzheimer's Disease Assessment Scale, cognitive portion) in a mixed group comprising 72 AD and 12 MCI patients after a 1-year program of cognitive-motor stimulation plus psychosocial compared with psychosocial support. In a small-scale (n = 18) RCT trial, Rapp et al [9] compared cognitive intervention with no treatment. They reported improved subjective memory and long-term maintenance during a 6-month period but no effect on objective tests of memory. Gunther et al [10] reported long-term improvement in cognitive performance (working memory and verbal episodic memory) in a pre-post comparison study of computer-assisted cognitive training in persons with MCI. Finally, Belleville et al [11] compared the effect of a multifactorial memory training program with a no-training condition (28 MCI participants) and reported larger memory improvement on post-test in the trained MCI participants compared with the untrained ones. Moderate to large effect sizes were obtained for the training effect on target episodic memory measures. Thus, studies investigating the effect of cognitive intervention in MCI provide encouraging findings. However, the effort required to implement such therapeutic measures is not trivial, and large scale cognitive intervention for MCI would require considerable resources. Before widespread recommendation of this therapy can occur, more replication studies are required with properly controlled RCT designs, larger sample sizes, and analyses that control for type 1 error.

In conclusion, longitudinal cohort studies of healthy older adults indicate that engagement in intellectually stimulating activities is associated with decreased risk of AD and decreased cognitive decline. However, the evidence at the present time is insufficient to conclude that organized cognitive intervention is beneficial to preventing progression in MCI or warrants prescription. On the other hand, given that there is little or no "downside" to cognitive activity, it is not unreasonable for physicians and therapists to promote engagement in cognitive activity as part of an overall healthy lifestyle formulation for elderly individuals with and without memory loss.

2.2. Physical training in MCI

Several longitudinal cohort studies carried out in normal elderly individuals indicated that physical exercise is associated with reduced cognitive decline and reduced risk of dementia. These studies looked at outcomes such as a change score on the Mini-Mental State Examination