SYSTEMATIC REVIEW OF STRENGTHS AND LIMITATIONS OF RANDOMIZED CONTROLLED TRIALS FOR NON-PHARMACOLOGICAL INTERVENTIONS IN MILD COGNITIVE IMPAIRMENT: FOCUS ON ALZHEIMER’S DISEASE

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Abstract: Background: Non-pharmacological interventions may improve cognition and quality of life, reduce disruptive behaviors, slow progression from Mild Cognitive Impairment (MCI) to dementia, and delay institutionalization. It is important to look at their trial designs as well as outcomes to understand the state of the evidence supporting non-pharmacological interventions in Alzheimer’s disease (AD). An analysis of trial design strengths and limitations may help researchers clarify treatment effect and design future studies of non-pharmacological interventions for MCI related to AD. Methods: A systematic review of the methodology of Randomized Controlled Trials (RCTs) targeting physical activity, cognitive interventions, and socialization among subjects with MCI in AD reported until March 2014 was undertaken. The primary outcome was CONSORT 2010 reporting quality. Secondary outcomes were qualitative assessments of specific methodology problems. Results: 23 RCT studies met criteria for this review. Eight focused on physical activity, fourteen on cognitive interventions, and one on the effects of socialization. Most studies found a benefit with the intervention compared to control. CONSORT reporting quality of physical activity interventions was higher than that of cognitive interventions. Reporting quality of recent studies was higher than older studies, particularly with respect to sample size, control characteristics, and methodology of intervention training and delivery. However, the heterogeneity of subjects identified as having MCI and variability in interventions and outcomes continued to limit generalizability. Conclusions: The role for non-pharmacological interventions targeting MCI is promising. Future studies of RCTs for non-pharmacological interventions targeting MCI related to AD may benefit by addressing design limitations.

Key words: Mild cognitive impairment, Alzheimer’s disease, non-pharmacologic interventions, physical activity, cognitive interventions, socialization, randomized controlled trial, CONSORT score.

Introduction

There is neither a cure nor a disease modifying drug for Alzheimer’s disease. Non-pharmacological interventions are therefore essential to managing elders with this progressive, neurodegenerative disorder. Mild Cognitive Impairment (also known by the DSM-V criteria as Mild Neurocognitive Disorder) (1) is a dynamic, early clinical stage of AD, with objective neurocognitive deficits but preserved daily function. Annual conversion rates from MCI to dementia are reported between 8.1% and 6.8% (2). Persons with dementia (also known by the DSM-V criteria as Major Neurocognitive Disorder) (1) have functional deficits and require assistance with at least one activity of daily living. Once individuals reach the stage of dementia, they are more likely to be hospitalized, and each hospitalization is likely to be more costly (3). Average cost of chronic conditions such as heart failure and diabetes are higher in elders with dementia (4). These patients need caregivers, and those caregivers have a higher risk for depression and dementia than non-caregivers (5). Non-pharmacological interventions that promise to reduce the progression of MCI to dementia could improve quality of life for both patients and caregivers and reduce care costs.

Several observational longitudinal and cross-sectional studies have shown that the rate of cognitive decline towards dementia can be modified by cognitive and lifestyle factors, including cognitively engaging activities, physical exercise and socialization (6, 7). Several biologically plausible models support preservation of cognitive function with age (8-11) and similar studies have been reported in AD mouse models (12-15). Despite these observations, extension of non-pharmacological intervention clinical trials to elders with cognitive impairment is often challenging to operationalize due to multiple confounders. We have systematically reviewed the methodology of randomized clinical trials (RCTs) for non-pharmacological interventions in MCI, focusing on cognitive impairments related to underlying AD, to identify their strengths and challenges in designing clinical trials and interpreting outcomes.

Methodology and rationale for review

RCTs targeting cognitive interventions, physical activity, and socialization were the focus of this review. Cognitive training...
is the goal-oriented practice of a specific structured cognitive task with the intention of limiting deterioration in cognition and function. Physical activity and socialization are lifestyle interventions in MCI with the same purpose, to delay decline in cognition and function. Studies of dietary interventions including effects of diet and supplements were excluded due to extensive reviews in the literature on these studies. Studies of psychotherapeutic interventions (mindfulness, relaxation, stress reduction, and sleep interventions) and compensatory strategies were excluded due to known difficulties in design and evaluation due to multiple confounders, including selection bias, diffusion or imitation of intervention, experimenter expectancy, compensatory expectancy of treatments (16), the degree of subject engagement in the intervention, and the Hawthorne effect (17).

We searched PubMed, PsycINFO and SCOPUS for studies exploring the effects of the targeted non-pharmacological interventions on cognitive outcomes in MCI (including all diagnostic criteria for MCI) using search terms: 1. “cognitive intervention” or “cognitive activity” or “cognitive rehabilitation” or “cognitive exercise” 2. “physical activity” or “exercise” 3. “socialization” or “social activity” AND “mild cognitive impairment”. All titles and abstracts that were search hits from January 2000 until March 31, 2014 were reviewed to eliminate studies that did not pertain to our topic of interest. Reference lists were also reviewed to identify additional studies. Articles included in the final review met the following criteria: 1) The study primarily evaluated a cognitive outcome of physical activity, cognitive intervention or socialization in MCI; 2) The study was a randomized controlled trial; 3) Inclusion and exclusion criteria for MCI were specified; 4) Adequate statistical measures with effect sizes were reported; 5) Cognitive measures were included as primary or secondary outcomes; 6) Non-pharmacological intervention was implemented as a single intervention in at least one arm of the trial. All studies were extracted and tabulated by one of the reviewers (TH) onto a standard template and reviewed by BMR and JP. Differences in opinions regarding inclusion were resolved by consensus.

The primary outcome of the systematic review was adherence of each study to the CONSORT 2010 reporting criteria (18). Higher-quality reports may be more likely to improve RCT interpretation, minimize biased conclusions, and ultimately facilitate decision making about treatment effectiveness. The CONSORT guidelines were originally published in 1996 to improve the quality of reporting results of RCTs, and have been updated periodically, most recently in 2010. We estimated adherence as a sum of individual items in the 37-item checklist contained in CONSORT 2010. Each CONSORT 2010 item was assigned a “1” if it were reported, and a “0” if it were not. The sum score was the estimated report quality measure, adapted from Huwiler-Muntener et al (19). Secondary outcomes of this systematic review were a qualitative analysis of methodological difficulties found in the design of the included trials.

Results

Twenty-three studies met our inclusion criteria. Of these studies, eight studies focused on physical activity (20-27), fourteen incorporated cognitive interventions (28-41), and one explored the effects of socialization (42). The details of the studies are in Tables 1-3.

Figure 1 depicts the CONSORT scores for all studies since 2000. Most studies demonstrate a positive effect compared with control. As depicted in Figure 2, the mean CONSORT reporting quality score for physical activity interventions, 31.5(SD 5.2), was statistically higher than the mean quality score for cognitive interventions, 25.4(SD 3.5) (p < .013, Independent samples t-test, equal variances not assumed). The overall mean, including the one socialization study, was 27.7 out of 37 (range: 20 to 37, SD 5). Separating the CONSORT scores by intervention, Figure 3 demonstrates an improvement in CONSORT quality scores since 2000 among physical activity interventions, but not, as in Figure 4, in cognitive interventions. In both the cognitive and physical activity interventions, there was an overall improvement in enrollment of larger pool of subjects and longer duration of intervention and follow-up. However, the cognitive domains (executive, delayed recall, attention) chosen as outcomes were inconsistent across studies even when studies within a single modality of intervention (cognitive or physical) were analyzed.

Figure

Survey of physical, cognitive and socialization interventions. The number of subjects in each study relates to log circumference of point size

Given the difference in pattern of CONSORT scores, we analyzed each type of intervention separately.

Physical activity interventions

The mean reporting score was higher for physical activity interventions compared with cognitive interventions. The physical activity interventions tested included different degrees