

# Is there an effective disease-modifying treatment for Parkinson's mild cognitive impairment (PD-MCI)?

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## Clinical bottom line

Recent systematic reviews and meta-analyses evaluating the effect of exercise programmes,<sup>1</sup> meditation,<sup>2</sup> cognitive rehabilitation,<sup>3</sup> cognitive training,<sup>4</sup> non-invasive brain stimulation<sup>4</sup> and exergaming<sup>5</sup> did not yield evidence that was sufficiently robust to recommend any as disease-modifying treatment for PD-MCI.

## Background

Given the profound impact of Parkinson's dementia (PDD) on the patient<sup>6</sup> and any carers,<sup>7</sup> there is interest in treating PD-MCI to avert progression to PDD. This CAT aimed to explore the evidence in favour of disease-modifying treatments for PD-MCI. It was beyond the scope of the CAT to critically appraise all relevant clinical trials. Therefore, the search was restricted to systematic reviews (including meta-analyses).

## Search terms

"Parkinson's disease" AND "cognitive impairment"

## Search strategy

A search was conducted for the most recent systematic reviews using PubMed Clinical Queries (category: therapy; scope: broad). No date restriction was applied. Studies about treatment of PDD, animal studies and studies in languages other than English were excluded. A hand-search of bibliography from key studies was also conducted.

## Evidence

From 104 systematic reviews, the most recent was selected for each intervention. This yielded systematic review or meta-analytic evidence for the following interventions: exercise programmes,<sup>1</sup> meditation,<sup>2</sup> cognitive rehabilitation,<sup>3</sup> cognitive training,<sup>4</sup> non-invasive brain stimulation,<sup>4</sup> exergaming,<sup>5</sup> cholinesterase inhibitors and memantine.<sup>8</sup> The meta-analysis on cholinesterase inhibitors and memantine did not have disaggregated data analysis for patients with PD-MCI and was therefore excluded. A cited meta-analysis evaluating the effect of these drugs<sup>9</sup> was checked for disaggregated data, but again, there were none. The included studies are summarised and critically appraised below.

da Silva FC, Iop RDR, de Oliveira LC, et al. Effects of physical exercise programs on cognitive function in Parkinson's disease patients: A systematic review of randomized controlled trials of the last 10 years. *PLoS One*. 2018;13(2):e0193113.

### Summary

A descriptive systematic review of the effects of physical exercise on cognitive function in Parkinson's. It included nine randomised controlled trials from the preceding 10 years. Patients had mild to moderate symptoms, and a mean disease duration ranging from 4.7 to 11.2 years. Four physical exercise programmes had positive effects (expressed as Cohen's d) on cognitive function: adapted tango (d=0.07) and cognitive training (Wii Fit™) combined with motor training (d=0.19) on global cognitive function; treadmill training on processing speed and sustained attention (d=0.03) and cognitive flexibility (d=0.42); and speed treadmill training (d=1.30) and mixed treadmill training (d=0.37) on cognition assessed on PDQ-39. The authors concluded that physical exercise programmes promote positive and significant effects on global cognitive function, processing speed, sustained attention and mental flexibility in Parkinson's patients, at a mild to moderate stage for patients with a six-year clinical diagnosis of Parkinson's. They highlighted a finding that speed treadmill training performed three times a week for about 60 minutes and for a period of 24 weeks produced larger improvements in cognition.

The following should be noted:

- No search was conducted for unpublished material, and no analysis for publication bias.
- There was too much heterogeneity in terms of the interventions and cognitive assessments to allow meta-analysis.
- One study cited as having a positive effect on cognition (adapted tango intervention) was of poor methodological quality.

- Only speed treadmill training on PDQ-39 yielded a good effect size (d=1.30). It was unclear whether the effect sizes for other interventions were clinically significant.
- The instrument used to assess the effect of treadmill training (PDQ-39) provides a measure of general health status.<sup>10</sup> A specific cognitive assessment tool would yield a more valid measure of the effect on cognition.
- Overall, the quality of this systematic review was poor. It provides very weak evidence for the effectiveness of exercise programmes to improve cognitive function in PD-MCI.

Last N, Tufts E, Auger LE. The Effects of Meditation on Grey Matter Atrophy and Neurodegeneration: A Systematic Review. *Journal of Alzheimer's disease: JAD*. 2017;56(1):275-286.

### Summary

A descriptive systematic review of the effect of meditation on grey matter volume and neurodegeneration, assessed by MRI scan. 13 studies were included, of which only one was conducted among patients with Parkinson's.<sup>11</sup> All 13 studies reported significant increases in grey matter volume in the intervention group, in many different regions of the brain.

The following should be noted:

- There was no search for unpublished material, and no analysis for publication bias.
- The language of included studies was restricted to English.
- There was no comment on the overall quality of included studies; nor were there any sensitivity analyses to assess the effect of excluding poor studies.
- There was much heterogeneity in terms of the type of meditation used and the regions of the brain found on MRI scan to have been affected.

- The single randomised, controlled trial conducted among patients with Parkinson's concluded that an eight-week mindfulness-based intervention (N=14) resulted in increased grey-matter density (GMD) in the amygdala, and hippocampus compared to controls receiving usual care (N=13). Exploratory whole brain analysis showed increased grey-matter density in the left and right caudate nucleus, the left occipital lobe at the lingual gyrus and cuneus, the left thalamus, and bilaterally in the temporo-parietal junction. Increases in grey-matter density were also found in the control group, in the left anterior lobe and dentate nucleus of the cerebellum. The control treatment was not validated for mindfulness-based interventions.
- Change in grey-matter volume and/or density on MRI scan is a "surrogate outcome" that does not necessarily translate to manifest clinical change.
- Overall, this systematic review was of low quality, and provided very weak evidence in favour of meditation in neurodegenerative disease generally, and of a mindfulness-based intervention in Parkinson's in particular.

**Diez-Cirarda M, Ojeda N, Pena J, et al. Long-term effects of cognitive rehabilitation on brain, functional outcome and cognition in Parkinson's disease. Eur J Neurol. 2018;25(1):5-12.**

### Summary

A descriptive systematic review of the effects of cognitive rehabilitation in Parkinson's. 13 studies were included, six of which were randomised controlled trials for efficacy in terms of improved cognition. Five RCTs resulted in an improvement in cognitive function versus controls. In the remaining RCT, the control group (using Nintendo Wii™ computer gaming with movement) improved attention compared to the cognitive rehabilitation group.

The following should be noted:

- Few bibliographic databases were searched. Searches were for terms appearing only in

the title of articles. There was no search for unpublished material. It was unclear whether there was any language restriction. There was no hand-search of reference lists for additional relevant articles.

- There was no description of criteria by which the quality of included studies was assessed.
- Interventions and outcomes were too heterogeneous to allow meta-analysis.
- No data were provided on the effect sizes or confidence intervals of included studies.
- Four of the five positive RCTs were limited by small sample size. The remaining RCT was limited by a self-reported test for cognition.
- All RCTs used different training programmes.
- Overall, this systematic review was of low quality, and provided weak evidence in favour of neurorehabilitation to improve cognition in Parkinson's.

**Lawrence BJ, Gasson N, Bucks RS, Troeung L, Loftus AM. Cognitive Training and Noninvasive Brain Stimulation for Cognition in Parkinson's Disease: A Meta-analysis. Neurorehabil Neural Repair. 2017;31(7):597-608.**

### Summary

A meta-analysis to determine the efficacy of controlled trials of standard cognitive training, tailored cognitive training, transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). It comprised 14 controlled trials. For executive function, the pooled effect size for standard and tailored cognitive training combined was small (Hedges'  $g = 0.42$ ; 95% CI 0.15-0.68); and for standard cognitive training alone it was medium ( $g = 0.51$ ; 95% CI 0.16-0.85). For attention/working memory, small pooled effect sizes were found for combined cognitive training ( $g = 0.23$ ; 95% CI 0.02-0.44) and for standard cognitive training alone ( $g = 0.29$ ; 95% CI 0.04-0.53). For memory, small pooled effect sizes were again found for combined cognitive training and for standard cognitive training alone. The only relevant study of tDCS was excluded because of missing data. None of the three included studies of rTMS yielded a significant effect size. It was

concluded that standard and tailored cognitive training may improve executive function, attention/working memory, and memory in Parkinson's.

The following points should be noted:

- A limited number of bibliographic databases were searched. There was no indication of whether a language restriction applied. Grey literature was searched but there was no search for unpublished material. There was, indeed, evidence of publication bias.
- Of the 14 included studies, only two had a low risk of bias; seven had an unclear risk; and five had a high risk.
- Only two studies included patients with cognitive impairment. There was no separate analysis for this population of patients.
- Overall, this meta-analysis was judged to be of moderate quality. The important limitations were potential publication bias, and that only two studies included patients with cognitive impairment. It provides poor evidence in favour of cognitive training for improving cognition in Parkinson's.

**Stanmore E, Stubbs B, Vancampfort D, de Bruin ED, Firth J. The effect of active video games on cognitive functioning in clinical and non-clinical populations: A meta-analysis of randomized controlled trials. *Neurosci Biobehav Rev.* 2017;78:34-43.**

## Summary

A meta-analysis to determine the effects of exergames on global cognition and individual cognitive domains in clinical and non-clinical populations. It comprised 17 RCTs. Exergames improved global cognition ( $g=0.436$ , 95% CI=0.18–0.69,  $p=0.001$ ) for healthy older adults and clinical populations with conditions associated with neurocognitive impairments when all analysed together. Effects among clinical populations were smaller ( $g=0.34$ , 95% CI=0.06–0.62,  $p=0.017$ ). Only three studies included patients with PD, and the meta-analysis did not include a separate analysis for Parkinson's. Domain-specific analyses found exergames improved executive functions, attentional processing and visuospatial skills.

The following points should be noted:

- There was no search for unpublished material. The search was limited to studies in English.
- Overall, the quality of this meta-analysis was good, but there was no disaggregated analysis for patients with Parkinson's. It therefore provides poor evidence of the effectiveness of exergaming on cognitive impairment in this population.

## References

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