Snips from the journals

Interventions for dementia and cognitive decline

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Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis (1).

Recently, several large randomised controlled trials regarding the treatment of cognitive impairment in Parkinson's Disease without dementia (CIND-PD) or dementia due to Parkinson's disease (PDD) and dementia with Lewy bodies (DLB) were completed. This is a systematic review that includes the recent reports to provide updated evidence for the treatments of CIND-PD, PDD and DLB.

The authors searched the Cochrane Dementia and Cognitive Improvement Group Specialised Register, Pubmed, Embase and other sources for eligible trials. They selected global impression and cognitive function as primary efficacy outcomes, and dropouts and adverse events as safety outcomes. Furthermore, Meta-analysis and trial sequential analysis (TSA) were also used.

Ten trials were included in this study. Cholinesterase inhibitors and memantine produced small global efficacy on clinicians' global impression of change (CGIC), from a weighted mean difference of -0.40 (95% CI -0.77 to -0.03) to -0.65 (95% CI -1.28 to -0.01); however, cholinesterase inhibitors but not memantine significantly improved cognition on Mini-Mental State Examination (MMSE), from 1.04 (95% CI 0.43 to 1.65) to 2.57 (95% CI 0.90 to 4.23). Additionally, both of them had good safety outcomes, although rivastigmine showed an increased risk of adverse events than placebo (risk ratio, RR 1.19, TSA adjusted 95% CI 1.04 to 1.36); these events were usually mild or moderate, and the risk disappeared on serious adverse events.

They conclude that Cholinesterase inhibitors and memantine slightly improve global impression; however, only cholinesterase inhibitors enhance cognitive function. Besides, all the drugs have good safety outcomes. The limited trials precluded the generalisation of these outcomes.

Statin use and incident dementia: A nationwide cohort study of Taiwan (2).

Statins are widely used in clinical treatment. However, a U.S. Food and Drug Administration issued health alert has raised concerns for the adverse effects of statin-

associated confusion and memory loss in the elderly. It is necessary to clarify the relationship between statin use and risk of incident dementia as well as whether class effects exist.

In this population-based retrospective cohort study, a total of 33,398 patients aged ≥ 60 years were selected from a subset of the Taiwan National Health Insurance Research Databases and followed up for tracking the occurrence of any type of dementia from 2000 to 2010. The Cox proportional hazards model was used.

Compared to non-users, statin users had a significantly lower risk of incident dementia (hazard ratio [HR], 0.78; 95% CI, 0.72-0.85, $p < 0.001$). Higher potency and a longer cumulative duration of statin use were associated with a reducing risk of dementia. After stratifying by gender, the risk of incident dementia was lower in female statin users (HR, 0.76; 95% CI, 0.68-0.85, $p < 0.001$) than in male statin users (HR, 0.86; 95% CI, 0.75-0.98, $p = 0.024$).

The authors conclude that statin use was associated with a significantly lower risk of dementia in elderly patients in Taiwan. The potency and the cumulative duration of statin used played critical roles.

It is noteworthy however that this is not a randomised control trial and Cochrane (2009) concludes that there is good evidence from two RCTs with 26,340 participants (HPS 2002 and PROSPER 2002) that statins given in late life to individuals at risk of vascular disease have no effect in preventing AD or dementia.

Physical activity reduces hippocampal atrophy in elders at genetic risk for Alzheimer's disease (3).

The authors examined the impact of physical activity (PA) on longitudinal change in hippocampal volume in cognitively intact older adults at varying genetic risk for the sporadic form of Alzheimer's disease (AD).

Hippocampal volume was measured from structural magnetic resonance imaging (MRI) scans administered at baseline and at an 18-month follow-up in 97 healthy, cognitively intact older adults. Participants were classified as High or Low PA based on a self-report questionnaire of frequency and intensity of exercise. Risk status was defined by the presence or absence of the apolipoprotein E-epsilon 4 (APOE- $\epsilon 4$) allele. Four subgroups were studied: Low Risk/High PA ($n = 24$), Low Risk/Low PA ($n = 34$), High Risk/High PA ($n = 22$), and High Risk/Low PA ($n = 17$).

Over the 18 month follow-up interval, hippocampal volume decreased by 3% in the High Risk/Low PA group, but remained stable in the three remaining groups. No main effects or interactions between genetic risk and PA were observed in control brain regions, including the caudate, amygdala, thalamus, pre-central gyrus, caudal middle frontal gyrus, cortical white matter (WM), and total gray matter (GM).

These findings suggest that PA may help to preserve hippocampal volume in individuals at increased genetic risk for AD. The protective effects of PA on hippocampal atrophy were not observed in individuals at low risk for AD. These data suggest that individuals at genetic risk for AD should be targeted for increased levels of PA as a means of reducing atrophy in a brain region critical for the formation of episodic memories.

Effects of Ginkgo biloba supplementation in Alzheimer's disease patients receiving cholinesterase inhibitors: Data from the ICTUS study (4).

The Cochrane review (2009) concludes that the evidence for Ginkgo biloba (Gb) having predictable and clinically significant benefits for people with dementia or cognitive impairment is inconsistent and unreliable.

This study evaluates whether the use of Gb is associated with additional cognitive and functional benefit in AD patients already in treatment with cholinesterase inhibitors (ChEIs). Data are from mild to moderate AD patients under ChEI treatment recruited in the Impact of Cholinergic Treatment Use (ICTUS) study. Mixed model analyses were performed to measure six-monthly modifications in the Mini Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) subscale score, and the Activities of Daily Living (ADL) scale over a follow-up period of one year with additional Gb supplementation. A total of 828 subjects were considered for the present analyses. Significantly different modifications at the MMSE score over the 12-month follow-up were reported between patients on combined therapy compared to those only taking ChEIs. On the contrary, the modification of the ADAS-Cog score between the two groups did not show statistically significant differences, although similar trends were noticed. No significant modifications of the two adopted outcome measures were observed at the mid-term 6-month evaluation. The modifications over time of the ADL score did not show statistically significant differences between the two groups of interest. They suggest that Gb may provide some added cognitive benefits in AD patients already under ChEIs treatment.

The clinical usefulness of such effects remains to be confirmed and clarified as the statistical significance is only in the MMSE scores and not in the ADAS-Cog or ADL scales.

Antioxidant nutrients and age-related cognitive decline: a systematic review of population-based cohort studies (5).

This is a systematic review of studies involving major antioxidant nutrients and change in cognitive performance, while paying special attention to their methodological quality. Abstracts were independently reviewed; studies were selected based on pre-specified criteria. Methodological quality of primary studies was assessed using a methodological checklist for cohort studies. Findings were presented using a narrative synthesis and tabulation of results.

Eight-hundred and fifty potentially eligible studies were identified; 10 met the inclusion criteria and were retained for data extraction and appraisal. The main supportive evidence came from two studies, both judged to be of high quality: The first observed an accelerated decline in global cognition, attention, and psychomotor speed over nine years, concomitant to a decrease in plasma selenium levels over the same period; the second study reported a slower rate of global cognitive decline over three years in persons in the highest quartile of intake of vitamins C, E, and carotenes. All associations persisted after adjustment for confounding factors. Evidence in favour of beneficial associations with higher dietary intake of vitamin E and flavonoids, as well as higher serum beta carotene levels came from further studies of only adequate quality.

The protective effects of antioxidant nutrients against decline in cognition in older people is likely although the supportive evidence is still limited in number. It is also noteworthy that Cochrane (2012) concludes that there is no convincing evidence that vitamin E is of benefit in the treatment of Alzheimer's Disease or Mild Cognitive Impairment.

Maintenance Cognitive Stimulation Therapy (CST) for dementia: A single-blind, multi-centre, randomized controlled trial of Maintenance CST vs. CST for dementia (6).

Psychological treatments for dementia are widely used in the UK and internationally, but only rarely have they been standardised, adequately evaluated or systematically implemented. There is increasing recognition that psychosocial interventions may have similar levels of effectiveness to medication, and both can be used in combination. Cognitive Stimulation Therapy (CST) is a seven week cognitive-based approach for dementia that has been shown to be beneficial for cognition and quality of life and is cost-effective, but there is less conclusive evidence for the effects of CST over an extended period.

This multi-centre, randomised controlled trial (RCT) to assess the effectiveness and cost-effectiveness of Maintenance CST groups for dementia compares an intervention group who receive CST for 7 weeks

followed by the Maintenance CST programme once a week for 24 weeks with the control group who receive CST for 7 weeks, followed by treatment as usual for 24 weeks.

The primary outcome measures are quality of life of persons with dementia assessed by the Quality of Life in Alzheimer's Disease (QoL-AD) and cognition assessed by the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog). Secondary outcomes include the mood, behaviour, activities of daily living and the ability to communicate in subjects, costs involved and caregiver health-related quality of life. Using a 5% significance level, comparison of 230 participants will yield 80% power to detect a standardised difference of 0.39 on the ADAS-Cog between the groups. The trial includes a cost-effectiveness analysis from a public sector perspective.

A pilot study of longer-term Maintenance CST, offering 16 weekly sessions of maintenance following the initial CST programme, previously found a significant improvement in cognitive function (MMSE) for those on the intervention group. The study identified the need for a large-scale, multi-centre RCT to define the potential longer-term benefits of continuing the therapy that would provide definitive evidence of the potential efficacy of maintenance CST and establish how the long-term benefits can be compared with anti-dementia drugs such as cholinesterase inhibitors.

Declaration of interest

None declared

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