Kan medicatie geheugenstoornissen voorkomen?

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• O’Brien J, Burns A. BAP Dementia Consensus Group. **Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology.** *J Psychopharmacol* 2011;25:997-1019
1. Review evidence for the clinical diagnosis of dementia and its subtypes and the role of investigations in improving diagnostic accuracy.

2. Assess the evidence for the efficacy of currently available anti-dementia drugs in all common types of dementia and, based on that, make clear recommendations for clinical practice.

3. Appraise the evidence for the efficacy of drugs for those with early cognitive impairments (mild cognitive impairment).

4. Appraise the evidence for drugs with potential to delay or prevent dementia, or modify its disease course.
Categories of evidence for causal relationships and treatment

• I Evidence from meta-analysis of randomized controlled trials, at least one large, good-quality, randomized controlled trial or replicated, smaller, randomized controlled trials

• II Evidence from small, non-replicated, randomized controlled trials, at least one controlled study without randomization or evidence from at least one other type of quasi-experimental study

• III Evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case-control studies

• IV Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Proposed categories of evidence for non-causal relationships

• I Evidence from large representative population samples
• II Evidence from small, well-designed, but not necessarily representative samples
• III Evidence from non-representative surveys, case reports
• IV Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Strength of recommendation

• A Directly based on category I evidence
• B Directly based on category II evidence or extrapolated recommendation from category I evidence
• C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
• D Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence
Assessment and diagnosis

• Making a diagnosis of dementia subtype
  – There is type I evidence that the clinical diagnosis of dementia subtype
    according to internationally agreed consensus criteria is accurate, but
    some of the newly proposed criteria still require validation. (A)

• Use of structural brain imaging for diagnosis
  – There is type I evidence that CT or MRI should be used to exclude other
    cerebral pathologies and to help establish the subtype diagnosis. (A)

• Use of SPECT or PET imaging
  – There is type I evidence that perfusion (HMPAO) SPECT or FDG PET
    can differentiate between AD, VaD and FTD. (A)
  – There is type I evidence that dopaminergic SPECT or PET imaging can
    help differentiate DLB from AD. (A)

• CSF biomarkers
  – There is type II evidence that CSF markers of amyloid and tau
    may be useful diagnostic markers for Alzheimer’s disease, but
    further standardization and validation is required before they can
    be used clinically. (B)
Alzheimer’s disease

• **Treatment with cholinesterase inhibitors and memantine**
  – There is type I evidence for the efficacy of cholinesterase inhibitors in the treatment of mild to moderate Alzheimer’s disease and type I evidence for memantine in moderate to severe Alzheimer’s disease. (A)

• **Switching between cholinesterase inhibitors**
  – There is type II evidence to support the switching of one cholinesterase inhibitor to another if the first is not tolerated or effective. (B)

• **Combination therapy**
  – There is type II evidence for adding memantine to a cholinesterase inhibitor, but also a negative type 1b study. Until further studies are available the benefits of combination therapy are unclear. (B)
Dementia with Lewy bodies

• **Cholinesterase inhibitors**
  – There is type I evidence to support treatment with cholinesterase inhibitors in Lewy body dementia, both dementia with Lewy bodies and Parkinson’s disease dementia and that both cognitive and neuropsychiatric symptoms improve. (A)
  – There is type II evidence to support equal efficacy of all three cholinesterase inhibitors. (B)

• **Memantine**
  – There is type II evidence that memantine may produce cognitive and global improvements. (B)
Vascular dementia

• Treatment with cholinesterase inhibitors and memantine
  – There is type I evidence showing small cognitive improvements with both cholinesterase inhibitors and memantine in vascular dementia. However, benefits in terms of global outcome are not seen and adverse events for cholinesterase inhibitors (but not memantine) are significantly greater than placebo. Evidence indicates that neither cholinesterase inhibitors nor memantine should be prescribed to people with vascular dementia, though those with mixed VaD and Alzheimer’s disease may benefit. (A)
Frontotemporal dementia

• **Cholinesterase inhibitors**
  – There is type I evidence that cholinesterase inhibitors are not recommended for the treatment of frontotemporal dementia. (A)

• **SSRIs**
  – There is type II evidence that SSRIs may help some behavioural aspects of frontotemporal dementia, but do not improve cognition. Studies are mixed and further evidence is needed. (A)
Progressive supranuclear palsy

• Cholinesterase inhibitors
  – There is type II evidence that cholinesterase inhibitors are not helpful in progressive supranuclear palsy.

No treatments can be recommended at the current time. (B)
Mild cognitive impairment

• Treatment with cholinesterase inhibitors and vitamin E
  – There is type I evidence that cholinesterase inhibitors are not effective in reducing the risk of developing Alzheimer’s disease and type I evidence that vitamin E is not effective in reducing the risk of Alzheimer’s disease. (A)
Other putative therapies for dementia

- Dimebon (latrepirdine)
- Ginko biloba
- Hormone replacement therapy
- Folate and vitamin B12
- Statins
- Treatment of hypertension/vascular factors
Dimebon (latrepirdine)

- 7 trials involving a total of 1697 participants were found and six were included in the quantitative analyses. No data were available from the seventh trial.
  - Three trials involving 1243 patients were included in analyses of efficacy outcomes, and four trials involving 1034 patients were included in analyses of safety and tolerability outcomes.
  - 5 trials were judged to be at high risk of bias due to selective outcome reporting and three to be at high risk of attrition bias. There was low quality evidence favouring latrepirdine on the Clinician's Interview-Based Impression of Change Plus Caregiver Input after 26 weeks (CIBIC-Plus) (MD -0.60, 95% CI -0.89 to -0.31, 1 study, P < 0.001).
  - Due to imprecision in the results, it was not possible to determine whether latrepirdine had any effect on cognition measured with the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog) (MD -1.49, 95% CI -3.47 to 0.49, 3 studies, P = 0.14) or the Mini-Mental State Examination (MMSE) (MD 0.59, 95% CI -0.94 to 2.11, 3 studies, P = 0.45), or on function measured with the Alzheimer's Disease Co-operative Study - Activities of Daily Living scale (ADCS-ADL) (MD 1.00, 95% CI -1.15 to 3.15, 3 studies, P = 0.36) at study endpoint (26 or 52 weeks). We considered the evidence provided on these outcomes to be of overall low quality.
Dimebon (latrepirdine)

- However, there was some high quality evidence showing a very small benefit of latrepirdine on the Neuropsychiatric Inventory (NPI) (MD -1.77, 95% CI -3.09 to -0.45, 3 studies, P = 0.009) at study endpoint (26 or 52 weeks).
- Additionally, moderate quality evidence suggested that latrepirdine and placebo were comparable in adverse events (RR 1.03, 95% CI 0.93 to 1.14, P = 0.51), serious adverse events (RR 0.86, 95% CI 0.55 to 1.35, P = 0.52), dropouts (RR 0.91, 95% CI 0.65 to 1.27, P = 0.57) and dropouts due to adverse events (RR 0.98, 95% CI 0.57 to 1.67, P = 0.93).

• This meta-analysis was limited by the small number of studies, imprecision, inconsistencies between studies and likelihood of bias.
• Nevertheless, the evidence to date suggests that while not associated with an increased risk of adverse events compared with placebo, there is no effect of latrepirdine on cognition and function in mild-to-moderate AD patients, though there appears to be a modest benefit for behaviour.

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Ginko biloba

- 36 trials were included but most were small and of duration less than three months.
- 9 trials were of six months duration (2016 patients). These longer trials were the more recent trials and generally were of adequate size, and conducted to a reasonable standard.
- Most trials tested the same standardised preparation of Ginkgo biloba, EGb 761, at different doses, which are classified as high or low. The results from the more recent trials showed inconsistent results for cognition, activities of daily living, mood, depression and carer burden.
- Of the 4 most recent trials to report results three found no difference between Ginkgo biloba and placebo, and one reported very large treatment effects in favour of Ginkgo biloba.
- There are no significant differences between Ginkgo biloba and placebo in the proportion of participants experiencing adverse events.
- A subgroup analysis including only patients diagnosed with Alzheimer's disease (925 patients from 9 trials) also showed no consistent pattern of any benefit associated with Ginkgo biloba.

- Ginkgo biloba appears to be safe in use with no excess side effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and publication bias cannot be excluded. The evidence that Ginkgo biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable.

Hormone replacement therapy

- A total of 5 trials including 210 women with AD were analysed. Meta-analyses showed that there was a limited positive effect from low dosage of conjugated equine estrogens (CEE, 0.625 mg once a day) but not from higher dosage (1.25 mg of CEE once a day) on the Mini-Mental Status Examination after 2 months (WMD=1.28, 95% C.I.=0.26 to 2.30, z=2.45, p<0.01) and the effect disappeared after 3, 6 and 12 months of treatment. This effect was small and not clinically relevant as there was only a difference of 1 point on average in comparison with the placebo users (the scale range is 0-30).

- There were also short-term effects of 1.25 mg of CEE on tests of concentration and executive function, namely the Trail Making Test-B (WMD=-40.90, 95% C.I.-79.29 to -2.51, z=2.09, p<0.05) and Digit Span backward (WMD=0.67, 95% C.I.=-0.01 to 1.34, z=1.94, p<0.05).

Hogervorst et al. Cochrane Database Syst Rev 2002 CD003799
Hormone replacement therapy

- With regard to memory, only cued delayed recall of a word list was positively affected by 2 months of transdermal diestradiol (E2) (WMD=6.50, 95% C.I.=4.04 to 8.96, z=5.19, p<0.0001). No HRT effects were seen on other word lists, Paragraph Recall or Paired Associate Learning. In addition, no effects were seen on visual memory, language functions, most speeded tests, clinical rating scales or depression.

- Controls had better performance on the delayed recall of the Paragraph Test (overall WMD=-0.45, 95% C.I.=-0.79 to -0.11, z=2.60, p<0.01) after 1 month and on Finger Tapping after 12 months (WMD=-3.90, 95% C.I.=-7.85 to 0.05, z=1.93, p<0.05). Clinicians also gave controls a better score on a dementia rating scale (CDR, overall WMD=0.35, 95% C.I.=0.01 to 0.69, z=1.99, p<0.05). After correction for multiple testing, only the short-term positive treatment effect of E2 on memory remained.

- Currently, HRT or ERT for cognitive improvement or maintenance is not indicated for women with AD. As no data were available on women with other types of dementia (e.g. vascular dementia) this remains to be investigated.
Hormone replacement therapy

- Further evidence on HRT on cognitive function in post-menopausal women has emerged concluded that ERT and HRT do not protect against cognitive ageing in older post-menopausal women and may increase the risk of dementia.
  
  DOI: 10.1002/14651858

- Randomized trials have also failed to find any clinically meaningful and consistent evidence of benefit in treating patients with pre-existing mild-moderate AD with oestrogen.

- A Cochrane review (of 7 trials including 251 women with AD) concluded HRT/ERT is not indicated in AD.
  
  Hogervorst et al. Cochrane Database Syst Rev 2009
  DOI: 10.1002/14651858
The timing hypothesis may explain the discrepancy between observational and RCTs

- Rocca WA (Neurodegener Dis. 2010;7:163-6)
  - Case control and cohort studies show a neuroprotective effect in the early menopause phase
  - Estrogen treatment in the late postmenopause phase is associated with an increased risk of dementia and cognitive decline
  - The neuroprotective effects of estrogen depend of age, type and stage of menopause
- Henderson V W (Biochim Biophys Acta. 2009)
  - Estrogen exposure in the early menopause raises the possibility of cognitive benefit later in life
  - After about the age of 65 years, hormone therapy increases dementia risk
  - Further research is needed to understand short term and long term effects but estrogen therapy should not be initiated after age 65 to prevent dementia or remediate cognitive aging.
Folate and Vitamin B12

- 6 trials using folic acid alone and two using folic acid combined with vitamin B12 and concluded there was no evidence that such treatments improved cognition in unselected older people with or without dementia.
  DOI: 10.1002/14651858

- However, one large, 3-year trial of folic acid supplementation in 818 older people with high homocysteine levels reported some cognitive benefits, but did not examine dementia outcome.

- Another Cochrane review has examined the use of vitamin B12 supplementation alone and identified 3 studies, all in people with dementia, none of which reported benefits from this intervention but all of which were small and of poor quality.
  Malouf R and Areosa Sastre A. Cochrane Database Syst Rev 2003
  DOI: 10.1002/14651858.

- Since these reviews, one study of combined high-dose folic acid, vitamin B12 and vitamin B6 has been reported. This study examined 409 subjects with normal homocysteine levels and with mild to moderate AD (MMSE 14–26) over 18 months and found no benefits on cognition but an unexpected increase in depression in the intervention group.
No evidence that other pharmacological approaches prevent Alzheimer’s disease

- Anti-inflammatory agents
- Aspirin
- Anti-oxidants
Anti-inflammatory agents do not prevent Alzheimer’s disease

• Epidemiological evidence (Skezely 2010)
  – Observational studies found an association of NSAID use and a reduced risk of AD
  – By contrast RCTs are not effective in treating or preventing AD
  – RCT with rofecoxib or naproxen does not slow cognitive decline in AD patients
• ADAPT trial. (Arch Neurol 2008;65:896-905)
  – RCT with naproxen or celecoxib does not improve cognitive function
• It is hypothesized that NSAIDs may be beneficial in normal brain but detrimental when the Abeta deposition process has started because of their inhibiting activity on microglia which mediates Abeta clearance.
  Imbimbo B. Expert Opin Investig 2009;18:1147-68
Statins: Randomised trials

- MRC/HBF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled study Lancet 2002; 360:7-22

- Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial Lancet 2002; 360:1623-30
  - No reduction of dementia or cognitive deficit
  - Limitations:
    - Short follow-up in PROSPER
    - No patients > 82 years
    - Cognition=secondary outcome

  - Negative results on cognition
Statins

- The two large studies (heart protection study (HPS) and PROSPER) examined the effects of statins on cognitive decline and dementia as secondary study endpoints in large numbers of subjects (HPS enrolled 20,536 subjects, PROSPER 5804 subjects). Neither found a significant effect of statin treatment on cognitive function.

- Recent studies investigating the use of statins in established AD have shown no consistent evidence of benefit.

• There is good evidence that statins given in late life to people at risk of vascular disease **do not prevent cognitive decline or dementia.**

DOI: 10.1002/14651858.
Prevention of dementia in controlled hypertension trials

- MRC (Prince et al.) BMJ 1996; 312: 801–5
- Syst-Eur (Forette et al.) Lancet 1998; 352: 1347–51
- PROGRESS (Tzourio et al.) Arch Intern Med 2003; 163:1069-1075
- SCOPE (Hansson et al.) J Hypertens 2003; 21:875-886
- HYVET (Peters et al.) LANCET 2008; 7:683-89
Blood pressure-lowering agents and dementia: conflicting evidence

- Two randomised placebo-controlled studies demonstrated a reduction in the incidence of dementia
  - Syst-Eur
    - Based on calcium-channel blocker nitrendipine possibly associated with ACE-inhibitor enalapril and/or diuretic
  - PROGRESS
    - Run on post-stroke patients and based on ACE-inhibitor perindopril and diuretic indapamide
      Tzourio et al. Arch Intern Med 2003; 163:1069-1075
Treatment of hypertension/vascular factors

- The Hypertension in the Very Elderly Trial (HYVET-COG) was conducted on patients aged 80 and above who had systolic hypertension (Beckett et al., 2008). The trial had to terminate early as interim analyses showed reduction in both stroke and total mortality in actively treated patients. However, the cognitive function sub-study (Peters et al., 2008) found no statistical differences between treatment and placebo groups regarding dementia incidence or cognitive decline. Thus, the results of the HYVET trial suggest that treatment of systolic hypertension is indicated also in very elderly individuals to decrease the risk of stroke and total mortality, while short-term treatment show no effect on the incidence of dementia.
  

- No RCT has shown that treatment of vascular risk factors decreases the risk of developing dementia, or slows progression of cognitive symptoms in individuals with MCI or dementia. However, there is a lack of long-term studies and also of RCTs investigating the effect on cognitive function of treatment of vascular risk factors in individuals with MCI or dementia.

- Irrespective of the effect on cognitive function, vascular risk factors should be treated due to the effect on cardiovascular and cerebrovascular disease.
Antihypertensive treatment and Alzheimer’s disease

- More studies are needed to confirm that the BP lowering agents may prevent Alzheimer’s disease.
- Incidence of dementia should constitute the primary outcome of future long term trials comparing different classes of antihypertensive drugs in order to better determine the mechanism of dementia prevention.
Disease modifying therapies

• **Metal protein attenuating compounds (MPAC)**
  
  – There is level II evidence of their effect on Alzheimer’s disease. These agents **should not be prescribed** until more data on safety and efficacy are available. (B)
    

• **Gamma secretase inhibition**
  
  – There is level I evidence that tarenflurbil is **not effective** in Alzheimer’s disease. (A)
    

• **Vaccination and immunization studies**
  
  – There is preliminary level II evidence of their effect in Alzheimer’s disease on some endpoints, but also level II evidence that amyloid lowering does not affect clinical course. Amyloid-lowering agents **should not be prescribed** until more data on safety and efficacy are available. (B)
    
Conclusions

• There is no evidence at present to support any pharmacotherapeutic intervention to prevent dementia. There is type II evidence that antihypertensive therapy may be helpful, but further studies are required. (B)

• Treatment of vascular risk factors
  – There is level III and IV evidence that vascular risk factors are inadequately recognized and managed in people with dementia, and that recognition and management should be as active as in those without dementia. (D)