A systematic review of the current evidence from randomised controlled trials on the impact of medication optimisation or pharmacological interventions on quantitative measures of cognitive function in geriatric patients

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Supplementary Material 1: PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Done
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3-4 & Supplementary 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3-4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 3-4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 3-4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 3-4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3-4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 3-4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 3-4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 3-4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3-4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 3-4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	na
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	na
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 3-4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 3-4
RESULTS			

Section and Topic	Item #	Checklist item	Location where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 4-6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 7
Study characteristics	17	Cite each included study and present its characteristics.	Page 7-9
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 6-7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 7-9 and supplementary 4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 6-8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	na
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 7-9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	Page 7-9
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7-9
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 7-9
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9-10
	23b	Discuss any limitations of the evidence included in the review.	Page 10-11
	23c	Discuss any limitations of the review processes used.	Page 10-11
	23d	Discuss implications of the results for practice, policy, and future research.	Page 10-11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Available on request
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	none
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 11
Competing interests	26	Declare any competing interests of review authors.	See title page or end of final manuscript
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	na

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplementary Material 2

PICOs and instructions for systematic review of:

Definitions of key terms:

Cognitive function

Cognitive testing

Dementia

Pharmacological approaches to prevent/treat cognitive impairment

Inappropriate prescribing and medication optimization

Polypharmacy

Aims:

To review the most reliable evidence on the impact of medication optimization or pharmacological interventions on quantitative measures of cognitive function in geriatric patients derived from randomized controlled trials

Patient population (P):

Geriatric patients: Age limit ≥80 or patients aged 65 years or older with significant (typical for geriatrics) comorbidities (such as arterial hypertension, heart failure, myocardial infarction, acute coronary syndrome, stroke, atrial fibrillation, COPD, osteoporosis, type II diabetes mellitus, dementia, behavioral and psychological symptoms of dementia, depression, bipolar disorder, insomnia, chronic pain, epilepsy, Parkinson's disease, incontinence, anemia)

Intervention/tool (I):

Medication review/drug treatment optimization or pharmacological interventions

Comparator (C):

(n/a)

Outcome (O):

Changes in cognitive function

Study design (S):

Randomized controlled trials

Search strategy:

(Neuropsychological Tests [Mesh] OR "Stroop test"[Title/Abstract] OR "Trail Making Test"[Title/Abstract] OR "Wisconsin Card Sorting Test"[Title/Abstract] OR "Wechsler Memory Scale"[Title/Abstract] OR "NEECHAM Confusion Scale"[Title/Abstract] OR "DOSS"[Title/Abstract] OR "Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery"[Title/Abstract] OR "Delirium Detection Score"[Title/Abstract] OR "Memorial Delirium Assessment Scale"[Title/Abstract] OR "Short Portable Mental Status Questionnaire"[Title/Abstract] OR "MMSE"[Title/Abstract] OR "Brief Alzheimer screen"[Title/Abstract] OR "Timed Test of Money Counting"[Title/Abstract] OR "TTMC"[Title/Abstract] OR "Montreal Cognitive Assessment"[Title/Abstract] OR "MoCA"[Title/Abstract] OR "Clock draw test"[Title/Abstract] OR "Clock Drawing test"[Title/Abstract] OR "clock-drawing test"[Title/Abstract] OR "3-item recall"[Title/Abstract] OR "SLUMS"[Title/Abstract] OR "Mini-Cog"[Title/Abstract] OR "BOMC"[Title/Abstract] OR "Global Deterioration Scale"[Title/Abstract] OR "Confusion Assessment Method"[Title/Abstract] OR "Serial 7's"[Title/Abstract] OR "Reisberg-Scale"[Title/Abstract] OR "DemTect"[Title/Abstract] OR "The 4 'A's Test"[Title/Abstract] OR "4AT"[Title/Abstract] OR "Abbreviated Mental Test"[Title/Abstract] OR "AMT-10"[Title/Abstract] OR "AMT-4"[Title/Abstract] OR "bCAM"[Title/Abstract] OR "short-CAM"[Title/Abstract] OR "months of the year backwards"[Title/Abstract] OR "MOTYB"[Title/Abstract] OR "informant Single Question in Delirium"[Title/Abstract] OR "Informant single screening questions for delirium and dementia"[Title/Abstract] OR "SQiD"[Title/Abstract] OR "six-Item-Screener"[Title/Abstract] OR "Bamberger Demenz-Screening test"[Title/Abstract] OR "BDST"[Title/Abstract] OR "Severe Mini Mental State Examination"[Title/Abstract] OR "TFDD"[Title/Abstract] OR "Syndrom-Kurz-Test"[Title/Abstract] OR "Nursing Delirium Screening Scale"[Title/Abstract] OR "Delirium Observation Screening Scale"[Title/Abstract] OR "RUDAS"[Title/Abstract] OR "mini-Addenbrooke's Cognitive Examination"[Title/Abstract] OR "Nurses' Observation Scale of Cognitive Abilities"[Title/Abstract] OR "NOSCA"[Title/Abstract]) AND ("Polypharmacy"[Mesh] OR Polypharmacy[Title/Abstract] OR polytherapy[Title/Abstract] OR polymedication[Title/Abstract] OR hyperpolypharmacy[Title/Abstract] OR "medication appropriateness"[Title/Abstract] OR overprescribing[Title/Abstract] OR multidrug[Title/Abstract] OR "medication*"[Title/Abstract] OR "multiple medications"[Title/Abstract] OR "multiple drug*"[Title/Abstract] OR "beers criteria"[Title/Abstract] OR "STOPP AND START"[Title/Abstract] OR "FORTA"[Title/Abstract] OR "Medication Appropriateness Index"[Title/Abstract] OR "Potentially Inappropriate Medication List"[Mesh] OR "Potentially Inappropriate Medication"[Title/Abstract] OR "Inappropriate Prescribing"[Mesh] OR "Inappropriate Prescribing"[Title/Abstract] OR "Drug Therapy, Combination"[Mesh] OR "Pharmaceutical Preparations"[Mesh] OR "pharmacotherapy"[TW] OR "pharmacist review"[TW] OR "pharmacist intervention"[TW] OR "pharmacist assessment"[TW] OR "pharmacist management"[TW] OR

"pharmacist evaluation"[TW] OR "clinical assessment tool"[Title/Abstract] OR "decision support system"[Title/Abstract]) AND (random* [Title/Abstract] OR RCT [Title/Abstract] OR controlled trial [Title/Abstract] OR "Randomized Controlled Trial" [Publication Type]) AND ("Homes for the aged" [MeSh] OR "frail elderly" [MeSh] OR "geriatric assessment"[MeSh] OR "Nursing homes" [MeSh] OR "Vulnerable Populations" [MeSh] OR "Activities of daily living"[MeSh] OR "Aged" [MeSh] OR "Aged, 80 and over"[MeSh] OR "Geriatrics"[MeSh] OR "Geriatric Nursing"[MeSh] OR "Geriatric Psychiatry"[MeSh] OR "Health Services for the Aged"[MeSh] OR "Aging" [MeSh] OR Homes for the aged[MeSh] OR "Alzheimer disease"[MeSh] OR "Cognition disorders"[MeSh] OR "Dementia"[MeSh] OR "cognitive frailty" [Title/Abstract] OR elder* [Title/Abstract] OR elder*[Title/Abstract] OR eldest[Title/Abstract] OR frail*[Title/Abstract] OR geriatri*[Title/Abstract] OR old age*[Title/Abstract] OR oldest[Title/Abstract] OR old people[Title/Abstract] OR older[Title/Abstract] OR senior*[Title/Abstract] OR older people[Title/Abstract] OR older subject*[Title/Abstract] OR older patient*[Title/Abstract] OR older age*[Title/Abstract] OR older adult*[Title/Abstract] OR older man[Title/Abstract] OR older men[Title/Abstract] OR older male*[Title/Abstract] OR older woman[Title/Abstract] OR older women[Title/Abstract] OR older female*[Title/Abstract] OR older population*[Title/Abstract] OR older person*[Title/Abstract] or "aged" [Title/Abstract] OR "aging"[Title/Abstract]OR "ageing"[Title/Abstract] OR "community-dwelling" [Title/Abstract] OR caregivers [Title/Abstract]OR caregiver[Title/Abstract] OR caregiver [Title/Abstract] OR senium[Title/Abstract] OR septuagenarian*[Title/Abstract] OR octagenarian*[Title/Abstract] OR octogenarian*[Title/Abstract] OR nonagenarian*[Title/Abstract] OR centarian*[Title/Abstract] OR centenarian*[Title/Abstract] OR supercentenarian*[Title/Abstract])

Filters:

Years considered:

January 1, 1900 - May 19, 2021

Supplementary Material 3

Search terms for MEDLINE

(Neuropsychological Tests [Mesh] OR "Stroop test"[Title/Abstract] OR "Trail Making Test"[Title/Abstract] OR "Wisconsin Card Sorting Test"[Title/Abstract] OR "Wechsler Memory Scale"[Title/Abstract] OR "NEECHAM Confusion Scale"[Title/Abstract] OR "DOSS"[Title/Abstract] OR "Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery"[Title/Abstract] OR "Delirium Detection Score"[Title/Abstract] OR "Memorial Delirium Assessment Scale"[Title/Abstract] OR "Short Portable Mental Status Questionnaire"[Title/Abstract] OR "MMSE"[Title/Abstract] OR "Brief Alzheimer screen"[Title/Abstract] OR "Timed Test of Money Counting"[Title/Abstract] OR "TTMC"[Title/Abstract] OR "Montreal Cognitive Assessment"[Title/Abstract] OR "MoCA"[Title/Abstract] OR "Clock draw test"[Title/Abstract] OR "Clock Drawing test"[Title/Abstract] OR "clock-drawing test"[Title/Abstract] OR "3-item recall"[Title/Abstract] OR "SLUMS"[Title/Abstract] OR "Mini-Cog"[Title/Abstract] OR "BOMC"[Title/Abstract] OR "Global Deterioration Scale"[Title/Abstract] OR "Confusion Assessment Method"[Title/Abstract] OR "Serial 7's"[Title/Abstract] OR "Reisberg-Scale"[Title/Abstract] OR "DemTect"[Title/Abstract] OR "The 4 'A's Test"[Title/Abstract] OR "4AT"[Title/Abstract] OR "Abbreviated Mental Test"[Title/Abstract] OR "AMT-10"[Title/Abstract] OR "AMT-4"[Title/Abstract] OR "bCAM"[Title/Abstract] OR "short-CAM"[Title/Abstract] OR "months of the year backwards"[Title/Abstract] OR "MOTYB"[Title/Abstract] OR "informant Single Question in Delirium"[Title/Abstract] OR "Informant single screening questions for delirium and dementia"[Title/Abstract] OR "SQiD"[Title/Abstract] OR "six-Item-Screener"[Title/Abstract] OR "Bamberger Demenz-Screening test"[Title/Abstract] OR "BDST"[Title/Abstract] OR "Severe Mini Mental State Examination"[Title/Abstract] OR "TFDD"[Title/Abstract] OR "Syndrom-Kurz-Test"[Title/Abstract] OR "Nursing Delirium Screening Scale"[Title/Abstract] OR "Delirium Observation Screening Scale"[Title/Abstract] OR "RUDAS"[Title/Abstract] OR "mini-Addenbrooke's Cognitive Examination"[Title/Abstract] OR "Nurses' Observation Scale of Cognitive Abilities"[Title/Abstract] OR "NOSCA"[Title/Abstract]) **AND** ("Polypharmacy"[Mesh] OR Polypharmacy[Title/Abstract] OR polytherapy[Title/Abstract] OR polymedication[Title/Abstract] OR hyperpolypharmacy[Title/Abstract] OR "medication appropriateness"[Title/Abstract] OR overprescribing[Title/Abstract] OR multidrug[Title/Abstract] OR "medication*"[Title/Abstract] OR "multiple medications"[Title/Abstract] OR "multiple drug*"[Title/Abstract] OR "beers criteria"[Title/Abstract] OR "STOPP AND START"[Title/Abstract] OR "FORTA"[Title/Abstract] OR "Medication Appropriateness Index"[Title/Abstract] OR "Potentially Inappropriate Medication List"[Mesh] OR "Potentially Inappropriate Medication"[Title/Abstract] OR "Inappropriate Prescribing"[Mesh] OR "Inappropriate Prescribing"[Title/Abstract] OR "Drug Therapy, Combination"[Mesh] OR "Pharmaceutical Preparations"[Mesh] OR "pharmacotherapy"[TW] OR "pharmacist review"[TW] OR "pharmacist intervention"[TW] OR "pharmacist assessment"[TW] OR "pharmacist management"[TW] OR "pharmacist evaluation"[TW] OR "clinical assessment tool"[Title/Abstract] OR "decision support system"[Title/Abstract]) **AND** (random* [Title/Abstract] OR RCT [Title/Abstract] OR controlled trial [Title/Abstract] OR "Randomized Controlled Trial" [Publication Type]) **AND** ("Homes for the aged" [MeSh] OR "frail elderly" [MeSh] OR "geriatric assessment"[MeSh] OR "Nursing homes" [MeSh] OR "Vulnerable Populations" [MeSh] OR "Activities of daily living"[MeSh] OR "Aged" [MeSh] OR "Aged, 80 and over"[MeSh] OR "Geriatrics"[MeSh] OR "Geriatric Nursing"[MeSh] OR "Geriatric Psychiatry"[MeSh] OR "Health Services for the Aged"[MeSh] OR "Aging" [MeSh] OR Homes for the aged[MeSh] OR "Alzheimer disease"[MeSh] OR "Cognition disorders"[MeSh] OR "Dementia"[MeSh] OR "cognitive frailty" [Title/Abstract] OR elder* [Title/Abstract] OR elder*[Title/Abstract] OR eldest[Title/Abstract] OR frail*[Title/Abstract] OR geriatri*[Title/Abstract] OR old age*[Title/Abstract] OR oldest[Title/Abstract] OR old

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Supplementary Material 4

Summary of randomized controlled trials on the impact of drug optimization or pharmacological interventions on quantitative measures of cognitive capacity in geriatric patients.

PMID/Author/Year	Type of population	Age mean (SD if provided)	Number of study participants	Women (%)	Outcome(s) relating to cognitive capacity	Intervention/ duration	Details on medication review/medication optimization	Positive outcome(s) relating to cognitive capacity	Jadad score *
11479391/R. Camicioli/2001	Functionally independent patients with idiopathic Parkinson's disease (PD) who responded to L-Dopa and reported motor fluctuations	66.7 (range: 57–75)	5	40	Cognitive testing: simple reaction time and choice reaction time Stroop test, covert orienting of spatial attention, and digit ordering. Self-assessed mood, anxiety, arousal or concentration	Patients were withdrawn from their usual antiparkinsonian medications. Afterwards, they were administered 0.2 mg/kg oral methylphenidate followed 30 minutes later by a 1-hour intravenous L-Dopa (2 mg/kg per h) infusion/3 days	Participants who reported benefit from L-Dopa/carbidopa and motor fluctuations were admitted and withdrawn from their usual antiparkinsonian medications. On 3 consecutive days in a randomized double-blinded fashion, they took 0.2 mg/kg oral methylphenidate or placebo followed 30 minutes later by a 1-hour intravenous L-Dopa (2 mg/kg per h) or placebo infusion. The three possible conditions (methylphenidate/placebo infusion, placebo/L-Dopa infusion, methylphenidate/L-Dopa infusion) were assigned in a random order by a research	Choice reaction time increased with L-Dopa treatment with or without concomitant methylphenidate, whereas methylphenidate alone improved choice reaction time (p = 0.049)	2

							pharmacist who prepared the medication		
17537289/S. J. P. M. Eussen/2007	Population based, screened for mild cobalamin deficiency	82 ± 5	202	25	Various tests including MMSE	Eligible participants were randomized to receive 24 weeks of treatment in a parallel group design with daily oral doses of 1000mg cobalamin, a combination of 1000mg cobalamin and 400mg folic acid, or a placebo capsule/ 24 weeks	Individuals were randomized to receive daily oral capsules with either 1000 mg cobalamin, or 1000 mg cobalamin plus 400 mg folic acid, or placebo for 24 weeks. Concentrations of homocysteine, methionine, choline, betaine and dimethylglycine were assessed before and after 12 and 24 weeks of treatment. Cognitive function, including domains of attention, construction, sensomotor speed, memory and executive function, was assessed before and after 24 weeks of treatment.	Participants with the largest increases in betaine concentrations showed a borderline significant (p = 0.07) higher memory performance compared to those without it. A tendency of participants with the largest increases in betaine concentrations to show the greatest improvement in memory function was observed.	5
16330624/M. G. Cole/2006	Hospitalized emergency department	77.5 (6.7) vs 78.5 (6.6)	157	69	Hamilton Depression Rating Scale (HAMD), the Medical Outcomes 36-item	The intervention involved consultation and Treatment (guideline oriented) by a psychiatrist and	Consultation and treatment by a psychiatrist and follow-up by a research nurse and the patient's family physician. Research assistants, blind to group allocation,	There were no clinically or statistically significant differences the 2 groups in HAMD	3

				Short Form (SF-36), the Diagnostic Interview Schedule (DIS), MMSE	follow-up by a research nurse and the patient's family physician/ Follow-ups at 3 and 6 months	collected data from the patients	or SF-36 scores or any of the secondary outcome measures.	
17600848/P. J. Connelly/2008	Outpatients with probable Alzheimer's Disease who were treated with a cholinesterase inhibitor	76.27 (6.23)	57	70.7	Response according to the NICE criteria, MMSE, DSST, and IADL and Social Behaviour (SB) subscales of NOSGER	Capsules of 1mg of folic acid or placebo, daily administered/6 months	Concurrent treatment with a ChI and either folic acid or placebo. The study capsule and ChI were administered on the same day. The choice of ChI was left to the treating physician	Significant difference in the change of IADL and SB scores (folate + 1.50 (SD 5.32) vs placebo -2.29 (SD 6.16), p = 0.03) 16/23 subjects receiving folic acid were classified as NICE responders compared to 7/18 placebo subjects (p=0.05)	5
16316485/E. Savaskan/2006	Hospitalized patients with AD with behavioural symptoms	82.1 (7.02)	22	68.2	NPI, CERAD neuropsychological test battery (which included the following tests: verbal fluency, modified Boston Naming Test, MMSE,	Quetiapine (25 – 200 mg) or haloperidol (0.5 – 4 mg) / 5 weeks	The dosage was increased weekly: 25 mg for quetiapine and 0.5 mg for haloperidol. All patients received a ChI as co-medication (galantamine 2 x 8 mg)	Quetiapine and haloperidol both reduced delusions and agitation. Quetiapine improved the subscales depression	2

					constructional praxis and recall, word-list memory, word-list recognition and recall), NOSGER			(p=0.031) and anxiety, and haloperidol increased aberrant motor activity. Both haloperidol and quetiapine improved word recall. Quetiapine had a significant positive effect on word-list memory (p=0.006).	
19770382/C. Legault/2009	Postmenopausal women aged 65 and older at increased risk for breast cancer	69.9 (4.2)	1498	100	A cognitive test battery: Global cognition screening, verbal knowledge, verbal fluency, memory (figural and verbal), attention and working memory, spatial ability, fine motor speed, evaluated 1 and 2-years post enrollment	Oral tamoxifen 20 mg/d or oral raloxifene 60 mg/d / maximum of 5 years	Tamoxifen 20 mg/d or raloxifene 60 mg/d in healthy postmenopausal women at increased risk of breast cancer	Global cognition, memory, visuospatial skills and verbal knowledge changed significant and independently of treatment. There were significant time effects across the three visits for some of the cognitive measures. Raloxifene was associated with higher scores compared with	2

								tamoxifen (p=0.04) on the List B interference trial (measure of verbal memory)	
20094015/A. Valen-Sendstad/2010	Alzheimer's disease (AD) female outpatients aged 65–89 years, followed at a memory clinic in a general hospital	65-89	55	100	Dementia Rating Scale, Mini Mental State Examination (MMSE), Word List Memory, constructional praxis, Wechsler Adult Intelligence Scale–Digit Symbol-Coding, Trail Making Test, Part Al; Modified Consortium to Establish a Registry for AD (CERAD) Boston Naming Test, evaluated 6 and 12-months post intervention	Oral estradiol 1mg/d and norethisterone 0.5 mg/d or placebo / 12 months	Randomly assigned to receive either 1-mg estradiol and 0.5-mg norethisterone or placebo once daily	No significant treatment effects between groups	3
32710658/K. S. Boockvar/2020	Acutely-ill long-term nursing home residents	81.7 (1.1)	219	65.3	Cognitive Performance Scale (CPS), Brief Interview of Mental Status (BIMS) during and 30 days after the end of	Hospital Elder Life Program adapted to long-term care, a multi-component intervention including	Medication review completed on 54 of 114 (47%) patients of intervention group; were made recommendations to reduce or stop 22 drugs among 17 patients. The	The mean BIMS for the total sample increased from 8.8 at baseline to 9.9 at the end of the acute illness (p	1

					the acute illness episode	medication review and recommendations to primary care providers regarding discontinuing or reducing medications associated with delirium, using the American Geriatrics Society Beers guidelines, versus usual care / from the onset until one week post-treatment of an acute illness (maximum for 3 weeks)	most common drugs were histamine receptor 2 blockers (45%), drugs for Parkinson's disease (27%), benzodiazepines (18%), and anticholinergics (9%). Six patients had a medication reduced or discontinued as a result of a recommendation.	< .001) and the mean CPS decreased from 1.8 to 1.6 (not significant), but no positive effect on the intervention group	
26446153/A. L. Juola/2015	Assisted living	83	227	70.9	Verbal fluency and clock drawing tests	The intervention was an educational intervention for nursing staff working in the intervention wards./two 4-h interactive training sessions based on constructive learning	Educational contents: Polypharmacy; Potentially harmful drugs and their adverse effects (psychotropics, drugs with anticholinergic properties, Beers' Criteria drugs, NSAIDs, PPIs); Beneficial drugs for institutionalized older people,	None	3

					theory to recognize harmful medications and adverse drug events/Follow-up at 6 and 12 months	common drug–drug interactions; the use of SFINX database; Drugs and renal failure; use of the Renbase database		
20224285/U. Cornelli/2010	Patients suffering from probable AD	75 (4.2) intervention vs. 74 (4.9) control	52	55.7	MMSE II score and a three-point scale for sleeping	One group was treated with antioxidant formula F at a dose of one ampule/day in the morning immediately before breakfast/6 months	All patients were undergoing treatment with 5 mg of donepezil. One group was treated with antioxidant formula F at a dose of one ampoule/day in the morning immediately before breakfast, and the other group was treated with placebo (excipients plus 500 mg of fructose and flavouring) at one ampoule/day	None	2
29346524/L. Romera-Liebana/2018	Community-dwelling adults aged older than 65	77.3	352	75.3	Neuropsychological performance as measured by Short and Medium-Term Verbal Memory, Animal Naming Test, evocation of words beginning with one explicit letter, designation of famous people's	Four component intervention/12 weeks	Four component intervention: exercise training, intake of high protein nutritional shakes, memory training, and medication review (following STOPP criteria, with special focus on psychotropic drugs). Control group received standard care. Both groups were also	Neurocognitive battery improved significantly in the intervention group as compared to the control group at 3- and 18-months follow-up	2

					names, Verbal designation of images and verbal abstraction of word pairs		given counselling regarding dietary habits, lifestyle recommendations, and domestic hazards	
29052691/H. Wouters/2017	Nursing home residents	83.5	426	67.6	Mini-Mental State Examination (MMSE), Neuropsychiatric Inventory–Nursing Home Version (NPI-NH)	Single Multidisciplinary Multistep Medication Review (3MR)/45 minutes	Single Multidisciplinary Multistep Medication Review (3MR)/ 45 minutes on average. Standard care in the control group	No difference between the intervention and control group	3
26301603/J. E. F. Moonen/2015	Community-dwelling older people	intervention 81.1 (4.3) vs. control 81.5 (4.6)	385	Intervention 23 vs. control 30	Overall cognition (compound score): computed if 5 of the following 6 tests were available: Stroop Color Word Test and Trail Making Test for executive functioning, 15-Word Verbal Learning Test and Visual Association Test for (immediate and delayed) verbal and picture memory and Letter-Digit Substitution Test	Discontinuation of antihypertensive medications/16 weeks	Discontinuation of antihypertensive medications over a 6-week period after randomisation using a withdrawal algorithm with outcome assessment at 16 weeks	"In older persons with mild cognitive deficits, discontinuation of antihypertensive treatment did not improve cognitive, psychological, or general daily functioning at the 16-week follow-up." (J. Moonen 2015)	3

					for psychomotor speed; MMSE				

* The Jadad score which is a scale to assess the methodological quality or risk of bias of clinical trials is calculated by using a three-item questionnaire. Drop-outs/withdrawals, randomization, blinding and the quality of latter two items are assessed. The derived score ranges from zero (very poor) to five (rigorous). Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;17:1-12.

Abbreviations: AD: Alzheimer's Disease, ChI : Cholinesterase Inhibitor, NICE : National Institute for Health and Care Excellence, MMSE : Mini-Mental State Examination, DSST : Digit Symbol Substitution Test, IADL : Instrumental Activities of Daily Living, SB : Social Behavior, NOSGER : Nurses Observation Scale for Geriatric Patients, CIT : citalopram, MPH : methylphenidate, HDRS : Hamilton Depression Rating Scale, WCST : Wisconsin Card Sorting Test, NPI : Neuropsychiatric Inventory, CERAD : Consortium to Establish a Registry for Alzheimer's Disease, NA: not available/provided; DAT: The human dopamine transporter, VNTR: variable number of tandem repeats