SYSTEMATIC REVIEW

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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Abstract

Background Cognitive decline is common in older people. Numerous studies point to the detrimental impact of polypharmacy and inappropriate medication on older people's cognitive function. Here we aim to systematically review evidence on the impact of medication optimisation and drug interventions on cognitive function in older adults.

Methods A systematic review was performed using MEDLINE and Web of Science on May 2021. Only randomised controlled trials (RCTs) addressing the impact of medication optimisation or pharmacological interventions on quantitative measures of cognitive function in older adults (aged > 65 years) were included. Single-drug interventions (e.g., on drugs for dementia) were excluded. The quality of the studies was assessed by using the Jadad score.

Results Thirteen studies met the inclusion criteria. In five studies a positive impact of the intervention on metric measures of cognitive function was observed. Only one study showed a significant improvement of cognitive function by medication optimisation. The remaining four positive studies tested methylphenidate, selective oestrogen receptor modulators, folic acid and antipsychotics. The mean Jadad score was low (2.7).

Conclusion This systematic review identified a small number of heterogenous RCTs investigating the impact of medication optimisation or pharmacological interventions on cognitive function. Five trials showed a positive impact on at least one aspect of cognitive function, with comprehensive medication optimisation not being more successful than focused drug interventions. More prospective trials are needed to specifically assess ways of limiting the negative impact of certain medication in particular and polypharmacy in general on cognitive function in older patients.

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Key Points

This systematic review included 13 heterogeneous studies evaluating the impact of medication optimisation or pharmacological interventions (excluding single-drug trials) on cognitive function.

Most of the studies did not include medication optimisation (e.g., listing approaches) as an intervention, but used pharmacological interventions instead.

Five of the trials showed a positive impact on aspects of cognitive function.

Overall, there are few high-quality studies evaluating the impact of medication optimisation or drug interventions on cognitive functioning.

The improvement of cognitive function by these interventions should be addressed in future pharmacological studies.

1 Introduction

Cognitive decline is common in older people [1, 2], especially after acute hospitalisation [3]. While the pathogenesis of cognitive decline and cognitive impairment is multifactorial, there are numerous reports on the negative impact of polypharmacy (often defined as ≥ 5 daily medications) and inappropriate drug treatment on cognitive functioning in older adults [4–12]. For instance, the use of anticholinergics/antimuscarinics, antiepileptics or benzodiazepines has been linked with drug-induced cognitive impairment [13–15], which increases the risk of dementia and mortality in older adults [16–18]. Therefore, assessment of approaches towards medication optimisation and pharmacological interventions is urgently needed to evaluate whether cognitive decline can be prevented (or reversed) or whether cognitive function can be improved by such methods. Those proven to be effective could then be utilised in addition to numerous existing non-pharmacological approaches [19, 20].

In recent decades, several screening tools and listing approaches [21–23] designed to improve drug treatment (medication optimisation) in older people such as the Beers Criteria [24], STOPP (Screening Tool of Older Persons' Prescriptions)/START (Screening Tool to Alert to Right Treatment) criteria [25] and the FORTA (Fit fOR The Aged) list [26, 27] have been developed [21]. Previous studies have shown that most existing methods tested in randomised controlled trials were ineffective in improving clinical outcomes including those addressing cognitive function [21, 28]. Some trials, such as the trial using the FORTA list as an intervention, showed promising clinical effects on important parameters such as the Barthel index, but had no details on the intervention's effects on cognition [21]. In addition, the impact of pharmacological interventions such as the withdrawal of antihypertensive drugs on cognitive function has been tested in older people [29] but the results were uncertain.

So far, the established cognitive evaluation methods for assessing the impact of anti-dementia drugs on cognition [30, 31] have not been applied to the study of the impact of polypharmacy on cognitive function in multimorbid older people. An exception is the documented effect of certain prescribing cascade drugs on cognition, but these are mostly in the form of case reports [32, 33].

To our best knowledge, the number of randomised controlled trials (RCTs) on the impact of medication optimisation or pharmacological interventions (except for anti-dementia medication) on cognitive function in geriatric patients is limited. In this systematic review, we aimed to assess and summarise evidence from RCTs on the impact of interventions designed to attenuate polypharmacy and inappropriate drug treatment (medication optimisation) [22] and other pharmacological interventions apart from single drug trials (for example trials testing single drugs for dementia) on the quantitative measures of cognitive function in this vulnerable population. Since we were interested in all potential comprehensive interventions with a positive impact on cognitive function, pharmacological interventions were also included.

2 Methods

This systematic review was conducted according to the methodological manual of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA [34]). Details of the PRISMA checklist and "Population, Intervention, Comparison, Outcomes, Study design" (PICOS [35]) are provided in Supplementary Material 1 & 2. This systematic review was not previously registered in the PROSPERO database. The study was an initiative of the European Geriatric Medicine Society (EuGMS) special interest group (SIG) on Pharmacology.

2.1 Search Strategy

Search terms were proposed by two authors (FP and MW) to all EuGMS Pharmacology SIG members who agreed to participate in this study (N = 25). The search terms were discussed and amended accordingly. The final search terms as depicted in Supplementary Material 3, were used to search MEDLINE and Web of science. The search was

conducted on 19th May 2021 (end date). The start date was not restricted. The key elements in our search were cognitive function, drug treatment, geriatric patients, polypharmacy and inappropriate prescribing. In our search, only RCTs were included for analysis.

2.2 Inclusion Criteria

We included RCTs on the impact of medication optimisation or pharmacological interventions on pre-defined quantitative measures of cognitive function in geriatric patients. Geriatric patients were defined as follows: aged ≥ 80 years or patients aged ≥ 65 years with significant typical comorbidities defined by having 3 or more active diagnoses from a pre-defined list: arterial hypertension, heart failure, myocardial infarction, acute coronary syndrome, stroke, atrial fibrillation, chronic obstructive pulmonary disease (COPD), osteoporosis, type II diabetes mellitus, dementia, behavioural and psychological symptoms of dementia, depression, bipolar disorder, insomnia, chronic pain, epilepsy, Parkinson's disease, incontinence, anaemia. Thus, robust and active older people aged < 80 years were not included. A broad definition of medication optimisation [36] was used that included not only medication review, but also educational interventions, care coordination, use of technology (e.g., Computerized Clinical Decision Support), or 'brown bag' analyses. For the latter, a physician, pharmacist or nurse reviews patient's medications that have previously been put into a bag at home. For this purpose, patients need to put all of their prescription drugs, over-the-counter medicines (OTCs) and supplements that they are currently using into the bag.

2.3 Exclusion Criteria

Single drug interventions for drugs approved for treatment in the field of interest (e.g., single drug interventions for dementia or pain) were excluded. However, single drug group interventions such as those relating to withdrawal of antiepileptics or antipsychotics or drug interventions involving at least two drug substances were included. Studies exclusively describing non-geriatric patients were excluded as were studies without measurement of cognitive function. No exclusions were made regarding the language of the study unless the European study group (please see affiliations of all authors) was not able to understand the language (e.g., articles written in Chinese, Russian or Japanese).

2.4 Study Selection

The search results were exported from MEDLINE & Web of Science to EndNote® [37], duplicates were searched for and removed using EndNote® and ultimately, they were exported to Excel® files (Microsoft, Redmond, Washington).

Subsequently, 14 reviewers independently screened the titles (titles were divided between the reviewers) and abstracts of the manuscripts to identify relevant publications according to the inclusion/exclusion criteria. Abstracts were categorised as ineligible, possibly eligible, or clearly eligible. All abstracts chosen as clearly or possibly eligible for inclusion were screened by full-text analysis of the original publications in a second round by another reviewer independently. Records generating uncertainty regarding inclusion or exclusion criteria were discussed by FP and MW in order to reach consensus about inclusion.

2.5 Data Extraction and Synthesis

The following data were extracted from the selected publications: PubMed ID (PMID), first author, publication year, type of study population, mean age of study participants and standard deviation if provided, number of study participants, percentage of female participants, outcome(s) relating to cognitive function, brief description of the intervention and its duration, details on medication review/medication optimisation, positive outcome(s) relating to cognitive function. Methodological quality, or risk of bias of clinical trials, was assessed by using a three-item questionnaire, known as the Jadad score [38]. For the determination of the Jadad score, drop-outs/withdrawals, randomisation, blinding, and the quality of the latter two items are calculated and a score is derived ranging from 0 (very poor) to 5 (rigorous) [38]. In the evaluation of the RCTs, positive study outcomes corresponded to at least one primary or secondary endpoint exposing a significant improvement by the intervention (i.e., $p < 0.05$).

2.6 Measurement of Cognitive Function Considered for Study Selection and Data Extraction

The following terms/assessments (including common synonyms) were chosen by the authors to cover various quantitative measures of cognitive function:

Neuropsychological Tests, Stroop test, Trail Making Test, Wisconsin Card Sorting Test, Wechsler Memory Scale, NEECHAM Confusion Scale, DOSS, Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery, Delirium Detection Score, Memorial Delirium Assessment Scale, Short Portable Mental Status Questionnaire, Mini-Mental State Examination (MMSE), Brief Alzheimer screen, Timed Test of Money Counting (TTMC), Montreal Cognitive Assessment (MoCA), Clock draw test, Clock Drawing test, Clock-drawing test, 3-item recall, The Saint Louis University Mental Status (SLUMS), Mini-Cog, The Blessed Orientation-Memory-Concentration (BOMC), Global Deterioration Scale, Confusion Assessment Method, Serial sevens, Reisberg-Scale, Dementia detection

(DemTect), The 4 'A's Test (4AT), Abbreviated Mental Test (AMT-10, AMT-4), Brief Confusion Assessment Method (bCAM), The Short Confusion Assessment Method (short-CAM), months of the year backwards (MOTYB), Informant Single Question in Delirium, Informant single screening questions for delirium and dementia, The Single Question in Delirium (SQiD), Six-Item-Screener, Bamberger Demenz-Screening test (BDST), Severe Mini Mental State Examination, Test for early diagnosis of dementia with differentiation from depression (TFDD), Syndrom-Kurz-Test, Nursing Delirium Screening Scale, Delirium Observation Screening Scale, Rowland Universal Dementia Assessment Scale (RUDAS), Mini-Addenbrooke's Cognitive Examination, Nurses' Observation Scale of Cognitive Abilities (NOSCA).

In addition, using three or more cognitive tests in a study was regarded as a comprehensive testing of cognitive function.

3 Results

3.1 Study Selection

The search yielded 2568 publications, of which 2265 were excluded at the abstract assessment level (Fig. 1). The remaining 303 studies were reviewed in full-text: 290 were excluded based on the predefined criteria (vide supra), leading to the inclusion of 13 articles [39–51] in this systematic review.

The majority of the RCTs (10 of 13) used a comprehensive cognitive testing (3 or more tests) of cognitive function (Table 1). The total number of study participants, types of intervention, number of trials with positive outcome(s), and the number of trials with a Jadad score ≥ 3 (a trial with a score above 2 is considered to be of high quality [52]) are depicted in Table 1. In addition, a more comprehensive summary of all 13 RCTs found in this review is provided in Supplementary Material 4.

Among the 13 identified RCTs, five trials [39, 42–44, 49] reported a positive impact on at least one quantitative measure of cognitive function, though the quality of the majority of these positive trials was low (four had a Jadad score of only two). In contrast, the majority of all 13 trials (7 of 13) had a Jadad score of 3 or more.

Only 5 of 13 studies included a medication optimisation and of those, only 1 showed a significant impact on cognitive function [49] (Tables 1 and 2). In total, 4 of 5 trials used a specific listing approach (i.e., they used a specific structured method. These were Beers Criteria®, STOPP criteria and START criteria) as a method for medication optimisation [46, 47, 49, 50] and only one study [49] using the STOPP criteria as part of a multicomponent intervention showed a positive impact on cognitive function (measured

by a neurocognitive battery) of community-dwelling older people. In the study conducted by Cole et al [41], the intervention involved consultation and treatment by a psychiatrist and follow-up by a research nurse and the patient's family physician and no specific listing approach was used.

Five RCTs formally fulfilling the inclusion criteria had to be excluded as their readouts were related to depression [53–55] or BPSD/delusions [56, 57]. Dementia or related measures were inclusion or exclusion criteria in these trials; thus, they were detected by the search terms. Nevertheless, no measurements of aspects of cognition were reported in these trials.

3.2 Studies Addressing Aspects (≤ 2 Tests) of Cognitive Function (*N* = 3)

Juola et al [47] examined if educating nursing staff in assisted living facilities about harmful drug treatment has an impact on aspects of cognition as measured by verbal fluency and the clock drawing test; no significant difference between the groups was observed [47]. In this study, the nurses in the intervention group received two 4-h interactive training sessions to recognise potentially harmful medications and adverse drug events [47]. The Beers Criteria® was used in this trial.

Another study by Boockvar et al [46], which showed no impact on aspects of cognition also involved medication optimisation. In this trial, a multi-component intervention including medication review and recommendations to physicians regarding discontinuing or reducing medications associated with delirium was utilised. The Beers Criteria® were also used in this trial.

In contrast to the other two studies [46, 47], the trial by Cornelli et al [48] used a pharmacological intervention. But, similar to the other 2 studies, the intervention in this trial had no impact on aspects of cognition [48].

3.3 Studies Including a Comprehensive Testing (≥ 3 Tests) of Cognitive Function (*N* = 10)

In 5 out of 10 studies with a comprehensive testing of cognitive function a significant amelioration of cognitive function arising from a structured medication intervention was observed [39, 42–44, 49]. This intervention involved medication optimisation in only one study [49] and the remaining four were specific pharmacological treatments.

In one study of older patients with Parkinson's disease [39], involving withdrawal of patients from their usual antiparkinsonian drugs, short-term treatment with methylphenidate alone was preferable over subsequent short-term intravenous L-Dopa treatment (with or without concomitant methylphenidate) as measured by a significantly decreased choice reaction time in the methylphenidate only treatment
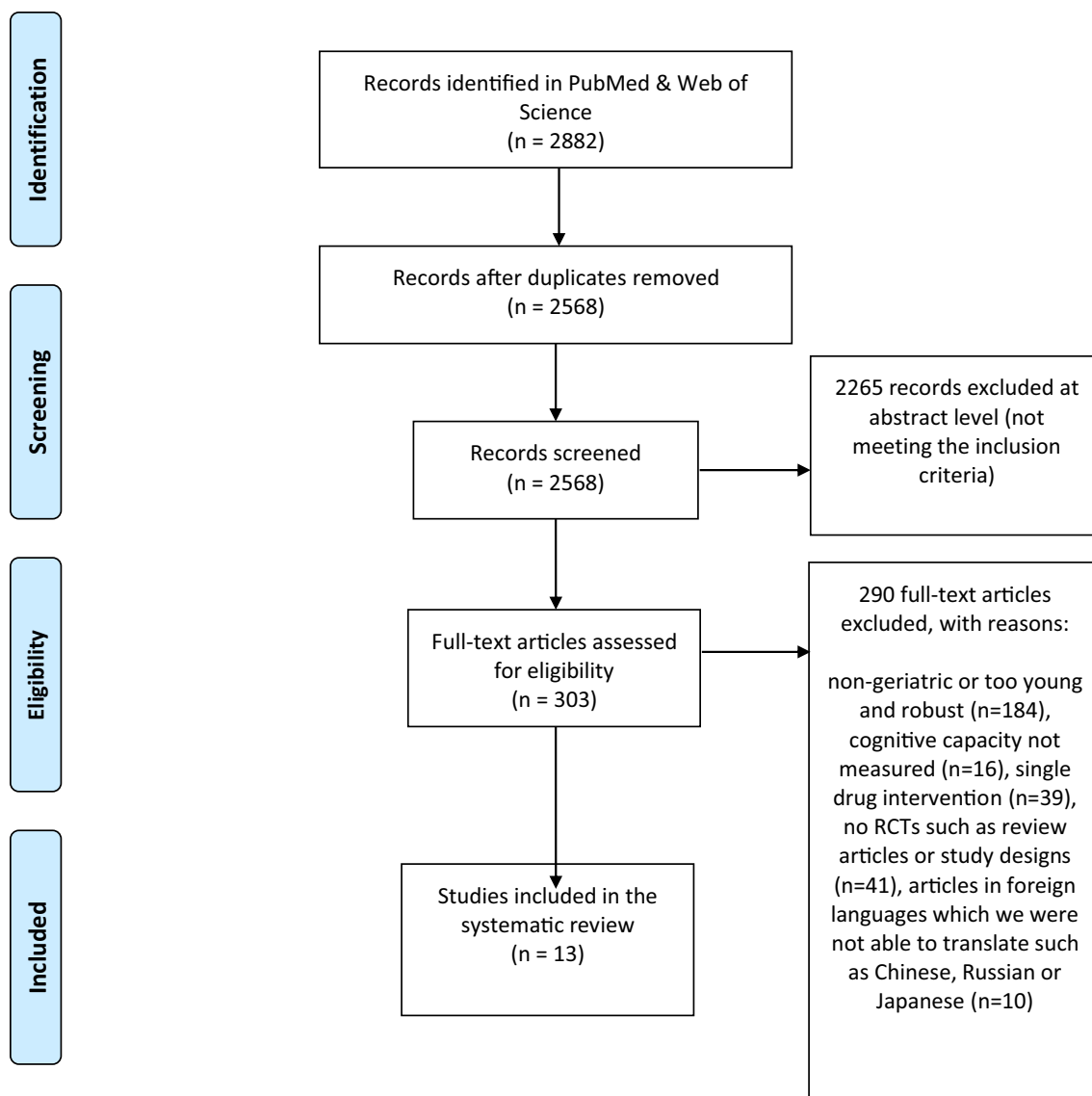
Fig. 1 Flow diagram of randomised controlled trials (RCTs) on the impact of medication optimisation or pharmacological interventions on quantitative measures of cognitive function in geriatric patients

(Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA])

group. No differences regarding the Stroop test, digit ordering, simple reaction time, or covert orienting of attention validity effect were observed. Changes in self-assessed analogue ratings of mood, anxiety, arousal, or concentration did not differ significantly between the groups.

Connelly et al [42] assessed the impact of folic acid in addition to acetylcholinesterase inhibitors (AChEI) on Mini-Mental State Examination (MMSE) and Social Behaviour (SB) subscales of Nurses' Observation Scale for Geriatric Patients (NOSGER) in patients with Alzheimer's Disease (AD). A significant difference was observed for the change from baseline in combined Instrumental Activities of Daily Living (IADL) and Social Behaviour scores between groups,

but no significant changes in MMSE scores were reported. This study indicated that response to AChEI in patients with AD may be improved by the concomitant use of folic acid.

A comparative study in patients with AD investigated the effects of quetiapine and haloperidol on various aspects of cognition [43]. In this study, a comprehensive psychometric test battery, including the Neuropsychiatric Inventory (NPI), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological evaluation schedule and NOSGER were used. Both quetiapine and haloperidol reduced delusions and agitation. Quetiapine improved the mean scores in the depression and anxiety subscales. Both haloperidol and quetiapine also improved word recall.

Table 1 Results of the systematic review on the impact of medication optimisation or pharmacological interventions on quantitative measures of cognitive function in geriatric patients

	Total number of trials	Number of study participants	Number of trials on pharmacological interventions[#]/ number of trials utilising medication optimisation[##]	Number of trials with positive outcome(s)	Number of studies with a Jadad score[*] of 3 or above
Interventional trials with aspects (1–2 tests) of cognitive function	3	498	1 2	0	1
Interventional trials with a comprehensive[$] testing of cognitive function	10	3159	7 3	5	6

[$]Three or more different tests of cognitive function were considered as comprehensive testing [#]Single-drug interventions for drugs approved for treatment in the particular field (for example, dementia, pain) were not included. However, "single drug group interventions" such as those with withdrawal of antiepileptics or antipsychotics or trials involving at least two drug substances were included

[##]A broad definition of medication optimisation was used including not only medication review, but also educational interventions, care coordination, use of technology, or 'brown bag' analyses

[*]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, randomisation, blinding and the quality of latter two items are assessed. The derived score ranges from zero (very poor) to five (rigorous) [38]

Quetiapine (but not haloperidol) had a significant positive effect on word-list memory.

A study in postmenopausal women compared the effects of tamoxifen and raloxifene on global and domain-specific cognitive function [44]. No differences were observed regarding global cognition, memory, visuospatial skills and verbal knowledge. However, there were significant time effects across the three visits for some of the cognitive measures. Compared to tamoxifen, raloxifene was associated with significantly higher scores for verbal memory.

In another study [49] utilising a multicomponent intervention consisting of exercise training, intake of high protein nutritional drink supplements, memory training, and medication review the neurocognitive battery test results improved significantly in the intervention group as compared to the control group at 3 and 18 months' follow-up.

In 5 studies, no significant impact of the intervention on comprehensive tests of cognitive function [40, 41, 45, 50, 51] was observed. In two of those studies the intervention included a medication optimisation [41, 50].

An overview of cognitive tests used in all 13 studies and the frequency and types of interventions with and without significantly positive impact on aspect(s) of cognitive function is summarised in Table 2.

We found no studies with a negative impact of an intervention on cognitive function.

4 Discussion

This systematic review revealed that approximately 40% of the included studies reported a positive impact on at least one quantitative measure of cognitive function in older people with multimorbidity and associated polypharmacy. This proportion was lower for those studies utilising medication optimisation as part of the interventional approach [49] (Tables 1 and 2). In total, only 4 trials used a specific listing approach as a method for medication optimisation [46, 47, 49, 50], and only one of those studies [49] using the STOPP criteria as part of a multicomponent intervention showed a positive impact on cognitive function in community-dwelling older people. Other components of the intervention in this particular trial included memory training, exercise training and intake of high protein nutritional shakes. Thus, the interventional impact on cognitive function that may be specifically attributed to medication optimisation remains unclear in this report. Indeed, non-pharmacological approaches to improve cognition such as memory training or even effective hydration care may play a more important role in this context.

Two studies using the Beers criteria [46, 47] or combining the START/STOPP and Beers Criteria did not report improved cognitive function [50]. It is therefore speculative at this time to suggest that a patient-focused approach requiring intricate knowledge of the patient (e.g., FORTA) might have been more successful in relation to achieving improved cognition in older people with multimorbidity and associated polypharmacy.

Based on the very low number of studies found, we debated on whether to include 4 additional RCTs [53–57] in this review. However, these studies assessed depression or BPSD/delusions as an endpoint and they did not report outcome measures of cognition.

It does not come as a surprise, and is in line with previous reports [21, 28, 58, 59], that the total number of studies examining the impact of medication optimisation

Table 2 An overview of cognitive tests and their frequency in the interventional studies included in this review and details on the interventions and assessments utilised in those studies

Number of cognitive tests	Number of studies (thereof pharmacological interventions)	Number of studies with positive outcome (thereof pharmacological interventions)	Intervention(s) and cognitive tests (underlined and in italics) used in the studies without impact (separated by a semicolon)	Intervention(s) and cognitive tests (underlined and in italics) used in the studies with positive outcome (separated by a semicolon)
1–2	3 (1)	0 (–)	A multi-component intervention including 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 [46] *Minimum Data Set Cognitive Performance Scale (MDS-CPS), Brief Interview of Mental Status (BIMS)*; Educational intervention for nursing staff working in the intervention wards/two 4-h interactive training sessions based on constructive learning theory to recognise harmful medications and adverse drug events [47] *Verbal fluency and clock drawing tests*; One group was treated with antioxidant formula F at a dose of one ampule/day in the morning immediately before breakfast [48] *MMSE II and a three-point scale for sleeping*;	–

Table 2 (continued)

Number of cognitive tests	Number of studies (thereof pharmacological interventions)	Number of studies with positive outcome (thereof pharmacological interventions)	Intervention(s) and cognitive tests (underlined and in italics) used in the studies without impact (separated by a semicolon)	Intervention(s) and cognitive tests (underlined and in italics) used in the studies with positive outcome (separated by a semicolon)
3 or more tests	10 (7)	5 (4)	In a parallel group design participants were randomised to receive 24 weeks of treatment with daily oral doses of 1000 mg cobalamin, a combination of 1000 mg cobalamin and 400 mg folic acid, or placebo [40]. _A neuropsychological test battery including MMSE;_ The intervention involved consultation and treatment by a psychiatrist and follow-up by a research nurse and the patient's family physician [41] _Hamilton Depression Rating Scale (HAMD), the Medical Outcomes 36-item Short Form (SF-36), the Diagnostic Interview Schedule (DIS), MMSE;_ Oral oestradiol 1 mg daily and norethisterone 0.5 mg daily or placebo [45] _Dementia Rating Scale, MMSE, Word List Memory, constructional praxis, Wechsler Adult Intelligence Scale–Digit Symbol-Coding, Trail Making Test, Part AlModified Consortium to Establish a Registry for AD (CERAD) Boston Naming Test;_ Single Multidisciplinary Multistep Medication Review (3MR) [50]. _MMSE Neuropsychiatric Inventory–Nursing Home Version (NPI-NH);_ Discontinuation of antihypertensive medications [51]. _MMSE & overall cognition (compound score): computed if 5 of the following 6 tests were available: Stroop Colour 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 for psychomotor speed_	Patients were withdrawn from their usual antiparkinsonian medications. On 3 consecutive days, they took 0.2 mg/kg oral methylphenidate or placebo followed 30 minutes later by a 1-h intravenous L-Dopa (2 mg/kg/h) or placebo infusion [39] _Simple reaction time and choice reaction time Stroop test, covert orienting of spatial attention, and digit ordering, Self-assessed mood, anxiety, arousal or concentration;_ Four component intervention: exercise training, intake of high protein nutritional shakes, memory training, and medication review. Control group received standard care. Both groups were also given counselling regarding dietary habits, lifestyle recommendations, and domestic hazards [49] _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 names. Verbal designation of images and verbal abstraction of word pairs;_ Concurrent treatment with a AChEI and either folic acid (1 mg capsule) or placebo [42] _Response according to the NICE criteria, MMSE, DSST, and IADL and Social Behaviour (SB) subscales of NOSGER;_ Treatment with Quetiapine (25–200 mg) or haloperidol (0.5–mg) in addition to cholinesterase inhibitors [43]. _NPI, CERAD neuropsychological test battery (which included the following tests: verbal fluency; modified Boston Naming Test, MMSE, constructional praxis and recall, word-list memory, word-list recognition and recall), NOSGER;_ Oral tamoxifen 20 mg per day or oral raloxifene 60 mg per day [44] _A cognitive test battery: Global cognition screening, verbal knowledge, verbal fluency, memory (figural and verbal), attention and working memory, spatial ability, fine motor speed_

MMSE mini-mental state examination, _DAT_ The human dopamine transporter, _VNTR_ variable number of tandem repeats, _AD_ Alzheimer's Disease, _AChEI_ Acetylcholinesterase Inhibitor, _NICE_ National Institute for Health and Care Excellence, _DSST_ Digit Symbol Substitution Test, _IADL_ Instrumental Activities of Daily Living, _NOSGER_ Nurses Observation Scale for Geriatric Patients, _HDRS_ Hamilton Depression Rating Scale, _WCST_ Wisconsin Card Sorting Test, _CERAD_ Consortium to Establish a Registry for Alzheimer's Disease. Pharmacological interventions: "single drug group interventions" such as those with withdrawal of antiepileptics or antipsychotics or trials involving at least two drug substances. Single drug interventions for drugs approved for treatment in the particular field (e.g., dementia, pain) were excluded

approaches on cognitive function is very limited and therefore the impact on this crucial geriatric outcome remains largely unclear.

The higher number of trials using pharmacological interventions when compared to medication optimisation approaches is notable. Those studies were heterogenous in nature and did not allow for direct comparisons. Nevertheless, half of them (4 of 8) showed a positive impact of the pharmacological intervention on cognitive function.

The compounds tested in the included studies of this systematic review (such as folic acid, cobalamin, sex steroids, selective oestrogen receptor modulators) were partially successful compared to placebo or a comparator, but none of those studies has the evidential power of changing medical practice or drug labelling. The Jadad scores were low (2.7) on average, and no follow-up or marketing approval studies for these hypothesis-generating RCTs could be detected in this review.

Despite the fact that the use of many medications has been associated with cognitive side effects in older adults, the number of RCTs examining approaches to improve cognitive functioning by optimising drug treatment is surprisingly low in this population with particular susceptibility to side effects of CNS drugs. This review shows that the complexity of reasons for cognitive impairment in older age is very challenging in regard to simple or more nuanced approaches to amelioration. Medication reviews, which could at least help to optimise drug treatment across all therapeutic areas, were not convincingly successful in this regard, although the optimal approaches to medication review towards cognitive protection still need to be tested.

Nevertheless, approximately 40% of the trials identified for inclusion in this systematic review showed a positive impact on aspect(s) of cognitive function. This indicates opportunities for improving cognitive function in older patients by medication optimisation or pharmacological interventions. However, these findings still need to be better explored and evaluated by further clinical trials.

4.1 Limitations

This systematic review was restricted to Web of Science and MEDLINE entries and to prespecified search terms. Therefore, relevant publications may have been overlooked. However, the likelihood of missing relevant studies with only one entry (if exclusively reported in Cochrane or Scopus, for example) was considered to be low as most studies typically have several detectable citations referring to each other. Also, unpublished trials were not searched for by contacting study investigators or sponsors. The analysis of results was primarily done by 14 investigators who could have partially misinterpreted data from RCTs. Finally, publication bias might exist, as trials with neutral or even negative effects on cognitive function may not have been published.

5 Conclusion

This systematic review indicates that the number of randomised controlled trials examining the impact of medication optimisation or pharmacological interventions on cognitive function is very limited and identified included studies are heterogenous and did not allow for direct comparisons or meta-analyses. About 40% of the trials showed a positive impact on at least one aspect of cognitive function. In the future, large-scale prospective high-quality clinical trials are needed to assess the impact of validated medication optimisation approaches or drug interventions on cognitive function using comprehensive assessment tools.

Declarations

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