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REVIEW

Impact of psychotropic medications on cognition among older adults: a systematic review

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ABSTRACT

Objectives: The aim of this systematic review is to examine the cognitive impact of psychotropic medications including benzodiazepines, antidepressants, mood stabilizers, antipsychotics, or a combination of these drugs on older adults.

Design: Systematic review.

Setting: We searched Medline, PsycINFO, and Embase through the Ovid platform, CINAHL through EBSCO, and Web of Science.

Participants and interventions: Randomized control trials (RCTs) and cohort studies that used a validated scale to measure cognition with a follow-up period of at least six months were included.

Measurement: The primary outcome of interest was cognitive change associated with psychotropic medication use.

Results: A total of 7551 articles were identified from the primary electronic literature search across the five databases after eliminating duplicates. Based on full-text analysis, 27 articles (two RCTs, 25 cohorts) met the inclusion criteria. Of these, nine each examined the impact of benzodiazepines and antidepressants, five examined psychotropic combinations, three on antipsychotic drugs, and one on the effects of mood stabilizers.

Conclusions: This is the first systematic review to examine the cognitive impact of multiple psychotropic drug classes in older adults over an extended follow-up period (six months or more) using robust sample sizes, drug-free control groups, and validated cognitive instruments. We found evidence to indicate cognitive decline with the cumulative use of benzodiazepines and the use of antidepressants, especially those with anticholinergic properties among older adults without cognitive impairment at baseline. Further, the use of antipsychotics and psychotropic combinations is also associated with cognitive decline in older adults.

Key words: antipsychotics, antidepressants, psychogeriatrics, cognitive disorders, psychopharmacology

Introduction

One in every four individuals over 65 years of age suffers from a mental illness, with anxiety disorder being the most common followed by mood and substance-related disorders (Andreas *et al.*, 2017). Therefore, psychotropic medications are often prescribed to older adults (Curkovic *et al.*, 2016). Older adults are also at a higher risk for cognitive decline with increasing age (Juan and Adlard, 2019; Lopez and Kuller, 2019). Thus, understanding the impact of psychotropic medications on cognition in older adults is key to any clinical or research attempt to prevent cognitive decline.

The role of anticholinergic medications in causing cognitive decline in the elderly is well known, and multiple psychotropic medications have anticholinergic properties (Boccardi *et al.*, 2017;

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Boustani *et al.*, 2008). However, psychotropic medications may also contribute to cognitive changes through other mechanisms (Snowden *et al.*, 2019). Dopamine is strongly linked with many cognitive processes; therefore, modulation of dopamine by psychotropic medications may cause changes in cognition (Nieoullon and Coquerel, 2003; Nieoullon, 2002; Snowden *et al.*, 2019). Similarly, the serotonergic system plays an important role in the regulation of mood and cognition and modulates neuroplasticity (Kraus *et al.*, 2017). Experimental depletion of tryptophan has been associated with a decline in episodic memory in healthy volunteers (Roiser *et al.*, 2007).

There is limited evidence on the impact of psychotropic medications on cognition in older adults, and the available evidence is mostly restricted to benzodiazepines and antidepressants (Wang *et al.*, 2016; Aldaz *et al.*, 2021; Bartels *et al.*, 2020; Pirker-Kees, *et al.*, 2019). Available evidence on benzodiazepine use in older adults has demonstrated some association between their use and cognitive decline, although this is not a consistent finding (Gerlach *et al.*, 2021; Osler and Jorgensen, 2020). Evidence on antidepressants has been more mixed, with some studies demonstrating slowing of cognitive decline but other research demonstrating accelerated decline or no change (Han *et al.*, 2020; Kodesh *et al.*, 2019; Wang *et al.*, 2016; Abdeljalil *et al.*, 2021). There is limited evidence on other psychotropic categories, although there is research demonstrating the negative cognitive impact of antipsychotics (Vigen *et al.*, 2011; Kim *et al.*, 2021; Tournier *et al.*, 2022).

Therefore, the objective of this systematic review is to comprehensively examine and compare the available published data on the cognitive impact of psychotropic medications including antidepressants, antipsychotics, benzodiazepines, mood stabilizers, and, or a combination of these drugs among older adults. We also assessed whether baseline characteristics influenced the cognitive impact of these medications.

Methods

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were used to guide this review. We included published randomized controlled trials (RCTs) and prospective and retrospective cohort studies. Studies in communities, hospitals, nursing homes, and mixed settings were included. We included studies with participants equal to or over 55 years of age, with control groups not exposed to psychotropic medication, a sample size of 50 or more individuals, a follow-up period of at least six months, and a validated cognitive assessment tool to appraise the changes in cognition. The age group of 55 and above was used to capture the pre-elderly who might be more vulnerable to the development of early cognitive changes with the use of psychotropic medications. We excluded case–control studies, cross-sectional studies, systematic reviews, meta-analyses, narrative review articles, protocols, editorials, commentaries, case series, and reports to ensure that only a higher level of evidence was included in the review.

Search strategy

The search strategy was iteratively developed by a medical librarian (FI) in collaboration with the research team. It was implemented on April 12, 2019, and revised again on April 22, 2022, in five electronic databases: Medline (including Epub ahead of print, in-process, and other non-indexed citations), PsycINFO, and Embase through the Ovid platform, CINAHL through EBSCO, and Web of Science. We did not apply any language or date limits.

The search strategy consisted of both subject headings and keywords associated with the concepts of cognitive impairment, psychotropic drugs, and the elderly. The McMaster University Health Information Research Unit (HIRU) review filter and the Scottish Intercollegiate Guidelines Network (SIGN) observational studies filter were used to limit the search. The search strategy was initially built in Medline and then translated as required for the other databases. Please refer to Appendix for the full strategy.

Study selection and data extraction

The first and second authors (SC and WUK) screened the titles and abstracts to assess eligibility for inclusion. SC and WUK reviewed full articles using the predetermined inclusion criterion and articles were selected based on mutual consensus. Data extraction was carried out by both authors using a standard data collection form. The following information was extracted from each study: author, year, sample size, setting, patient morbidity, drug used, control group, duration of follow-up, assessment tools, and outcomes.

The data were extracted independently by SC and WUK, and differences were discussed to reach a consensus. When consensus was not reached, the senior author TKR was available to arbitrate. We did not conduct a meta-analysis due to the heterogeneity among the studies, inconsistent quantitative data, and varied cognitive scales used as outcome measures.

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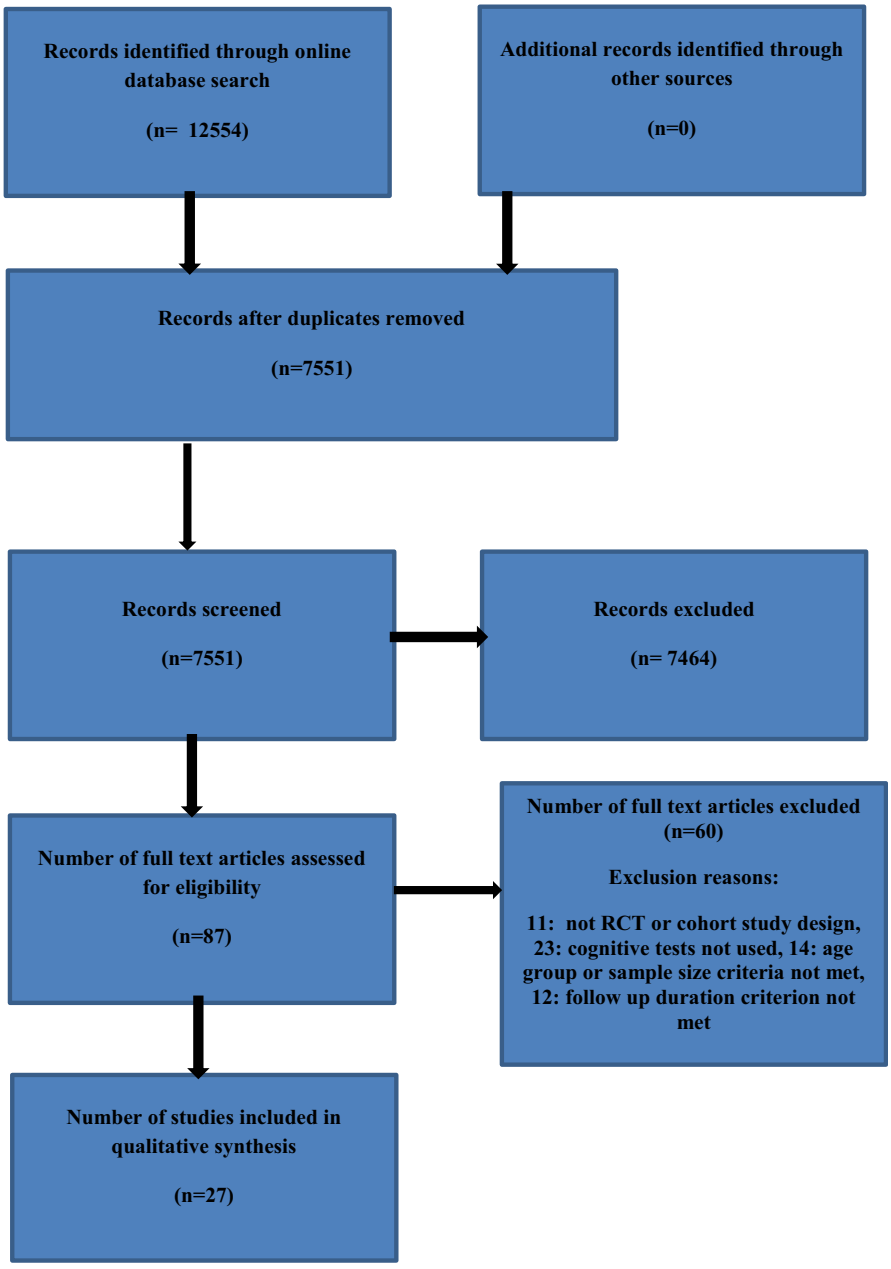

Figure 1. PRISMA flowchart.

Results

The strategy for the literature search is summarized in the flowchart (Figure 1). We identified 7,551 articles after eliminating duplicates. After reviewing titles, 444 articles remained; of which 87 full texts were retained after reviewing the titles and abstracts. After reviewing the full text, 27 articles were included in the full text. Of the 27 studies, nine reported on the cognitive impact of antidepressants, nine on benzodiazepines, three on antipsychotics, one on mood stabilizers, and five on a combination among these categories. Two of the studies were RCTs and 25 were cohort studies. The participants ranged from those with cognitively healthy older adults living in the community to those with advanced dementia living in nursing homes.

Description of studies

Antidepressants studies

Study settings

Nine studies (all cohorts) assessing the cognitive impact of antidepressants on older adults were included in the systematic review (Bartels *et al.*, 2018; Carriere *et al.*, 2015; Heath *et al.*, 2018; Heser *et al.*, 2018; Wang *et al.*, 2016; Goveas *et al.*, 2012; Caballero *et al.*, 2006a; Abdeljalil *et al.*, 2021; La

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et al., 2019). Six of the nine studies were in English-speaking countries, and three were in non-English-speaking European countries. All the studies were based in the community. Five of the nine studies were multicenter, of which three were based in various non-English speaking European countries. The length of the follow-up period varied from nine months to 12 years. Please refer to Table 1.

Participant details

One study focused on women alone, while all the other studies included both male and female participants (Goveas *et al.*, 2012). Three of the nine studies were on participants with preexisting cognitive impairments ranging from mild cognitive impairment (MCI) to moderate Alzheimer's disease, one study was on participants with varied cognitive states (normal cognition, MCI, or dementia), and the other five studies were on participants without cognitive impairment at baseline. Indications for the use of antidepressants were specified as depression and/or anxiety in some studies (Heath *et al.*, 2018; Bartels *et al.,* 2018), but not in others. The severity of depression at the time of follow-up was not documented in several of the studies (Heath *et al.*, 2018; Heser *et al.*, 2018), but was reported as euthymic at baseline and follow-up in one (Bartels *et al.,* 2018).

Medication details

One study focused on the use of trazodone alone (La *et al.*, 2019), one on selective serotonin reuptake inhibitors (SSRIs) alone (Bartels *et al.,* 2018), and the rest were on participants on multiple antidepressant categories.

Study outcomes

Of the five studies carried out on participants without cognitive impairment at baseline, one study reported an increased incidence of MCI of 70% with the use of antidepressants in this population (Goveas *et al.*, 2012). Three of the five studies demonstrated an increased incidence of dementia in antidepressant users (Wang *et al.*, 2016; Heath *et al.*, 2018; Heser *et al.*, 2018). The fifth study noted deficits in verbal fluency and psychomotor speed among antidepressant users at baseline, although no increase in dementia incidence was noted (Carrière *et al.*, 2017).

Of the three studies carried out on participants with cognitive impairment at baseline, two of the three reported no impact on cognition with antidepressant use (Abdeljalil *et al.*, 2021; Caballero *et al.*, 2006a). In the third study, Bartels *et al.* noted slower cognitive decline among participants with MCI with depression who used SSRIs for over four years, as compared to other participants who used SSRIs for shorter periods, those who used other antidepressants, or were antidepressant free. The only other study that demonstrated a positive result was conducted among participants with varied cognitive states ranging from normal cognition to dementia at baseline and focused on the use of trazodone (La *et al.*, 2019). This study noted slower cognitive decline among trazodone users as compared to nonusers, especially among those participants with sleep disturbance at baseline.

Medications associated with cognitive changes

Paroxetine and TCAs were noted to be associated with negative cognitive changes in several of the studies (Heser *et al.*, 2018; Heath *et al.*, 2018). Other studies noted cognitive decline with all antidepressant categories (Wang *et al.*, 2016; Goveas *et al.*, 2012; Caballero *et al.,* 2006a).

Benzodiazepine studies

Study settings

Nine studies (all cohorts) assessed the cognitive impact of benzodiazepines on the elderly. Three studies were in English-speaking countries, and the others were based in non-English-speaking European countries. Six of the nine studies were based in the community, one was in a nursing home (Bourgeois *et al.,* 2015), and the other two were in mixed settings (Desplenter *et al.*, 2012; Nafti *et al.*, 2020). Four studies were multicenter (Bierman *et al.*, 2007; Bourgeois *et al.*, 2015; Mura *et al.*, 2013; Nafti *et al.*, 2020). The period of follow-up ranged from 1 to 22 years. Please refer to Table 2.

Participant details

Gallacher *et al.* focused on older men alone, while all the other studies included both male and female participants. Eight out of the nine studies had participants without dementia at baseline, while one study had participants with a mix of cognitive presentations at baseline (Bourgeois *et al.*, 2015), who included only participants with Mini Mental State Examination (MMSE) scores of 18 and above, which might represent a population with early dementia, MCI, or no cognitive impairment.

Medication details

All studies focused on the use of benzodiazepines. However, Bourgeois *et al.* and Desplenter *et al.* included "Z-category drug" (zopiclone, zolpidem, zaleplon, and eszopiclone) users as well.

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Table 1. Impact of antidepressants on cognition

Author	Year	Type of study	Sample size (N) and age (mean)	Setting	Participant morbidity	Drug used	Control group	Duration of follow-up	Cognitive assessment tools	Outcome
Heser et al	2018	Prospective cohort	$N = 3239$, ≥ 75 years (79.62)	Germany; multicenter (6 cities); community-dwelling individuals	Without dementia	MAOI, SSRI, and other antidepressants	Antidepressant free	Up to 12 years	GDS; BDRS	Only antidepressants considered as potentially inappropriate medication were associated with an increased incidence of dementia ($p = 0.021$)
Heath et al	2018	Prospective cohort	$N = 3059$; $\geq$ 65 years	USA; community-dwelling individuals	Without dementia	TCAs, SSRIs, other antidepressants	Antidepressant free	Assessment every two years; mean follow-up of 7.7 years	CASI	Association between the use of paroxetine and the development of dementia was found at all levels of use, as measured by Total Standardized Daily Doses (TSDD). Hazard ratios ranged from 1.40–2.13 depending on the TSDD category
Bartels et al	2018	Prospective cohort	$N = 755$; 55–90 years (74.1)	Canada and USA; multicenter (50 sites); community-dwelling individuals	MCI or early Alzheimer's dementia	SSRI	Antidepressant free	Every six months or annually; mean follow-up of 691 days	MMSE; Rey Auditory Verbal Learning Test	A significant association between the use of SSRI >4 years in MCI patients with a history of depression and delayed progression to Alzheimer's dementia, as compared with short-term SSRI use ($p = 0.008$), other antidepressant use ($p \leq 0.001$), or no treatment
Carriere et al	2017	Prospective cohort	$n = 7381$; age ≥ 65 years	France; multicenter (3 cities); community-dwelling individuals	Without dementia	TCAs, SSRIs, and other antidepressants	Antidepressant free	Every two years; mean follow-up of eight years for patients not treated and 3.7 years for those treated with antidepressants	Isaac's Set Test; BVRT; TMT A and B; MMSE	No significant association was found between antidepressant use and cognitive decline

Table 1. Continued

AUTHOR	YEAR	TYPE OF STUDY	SAMPLE SIZE (N) AND AGE (MEAN)	SETTING	PARTICIPANT MORBIDITY	DRUG USED	CONTROL GROUP	DURATION OF FOLLOW-UP	COGNITIVE ASSESSMENT TOOLS	OUTCOME
Wang et al	2016	Retrospective cohort	$N = 3688$; age ≥ 60 years (67.9)	USA; Indiana; community-dwelling individuals	Without dementia	SSRIs, non-SSRI antidepressants	Antidepressant free	Two years	SPMSQ	Significant association noted between the use of antidepressants (SSRI and non-SSRI) and dementia as compared to non-users without depression (hazard ratio [HR] = 1.83, $p = 0.0025$ for SSRI users and HR = 1.50, $p = 0.004$ for non-SSRI users). SSRIs users had significantly higher dementia risk than non-users with severe depression (HR = 2.26, $p = 0.0005$)
Goveas et al	2012	Retrospective cohort	$N = 383$; age 65–79 years (71.0)	USA; 40 clinical centers; community-dwelling individuals	Cognitively healthy, post-menopausal women with depressive symptoms	SSRIs, TCAs, and other or multiple antidepressants	Antidepressant free	7.5 years	3MS	Antidepressant use was associated with a 70% increased risk of developing MCI. Both SSRIs and TCAs were associated with the development of MCI (SSRIs: hazard ratios (HR), 1.78 [95% CI, 1.01–3.13]; TCAs: HR, 1.78 [95% CI, 0.99–3.21])
Caballero et al	2006	Retrospective cohort	$N = 99$; age = cutoff not given, (70)	USA; Ohio State; community-dwelling individuals	Probable Alzheimer's disease	SSRIs and other antidepressants	Antidepressant free	Nine months	MMSE	No statistically significant difference was observed in MMSE scores for those taking antidepressants and not taking anti-depressants ($p > 0.05$).

Table 1. Continued

AUTHOR	YEAR	TYPE OF STUDY	SAMPLE SIZE (N) AND AGE (MEAN)	SETTING	PARTICIPANT MORBIDITY	DRUG USED	CONTROL GROUP	DURATION OF FOLLOW-UP	COGNITIVE ASSESSMENT TOOLS	OUTCOME
Abdeljalil et al	2021	Cohort	$N = 587$, mean age = 75 years	Europe: 12 countries; community-dwelling individuals	Mild-to- moderate Alzheimer's disease	SSRIs and other antidepressants	Antidepressant free	Two years with assessments done twice a year	MMSE and ADAS-Cog	No statistically significant difference was observed in MMSE or ADAS-Cog scores for those taking antidepressants and not taking antidepressants (MMSE: $p = 0.87$; ADAS-Cog: $p = 0.19$)
La et al	2018	Cohort	$N = 50$, mean age = 75.4 years	USA	Alzheimer's disease, MCI, or normal cognition	Trazodone	Trazodone free	Four years	MMSE	A statistically significant association between Trazodone use and delayed cognitive loss, with non-users having a 2.6-fold faster decline in MMSE scores as compared to users ($p = 0.023$)

GDS: Global Deterioration Scale, BDRS: Blessed Dementia Rating Scale, CASI: Cognitive Abilities Screening Instrument, MMSE: Mini-Mental State Examination, ADAS-Cog: Alzheimer's Disease Assessment Scale - Cognitive subscale, 3MS: Modified Mini-Mental State Examination, SPMSQ: Short Portable Mental Status Questionnaire, TMT: Trail Making Test, BVRT: Benton's Visual Retention Test, SSRI; Selective Serotonin Reuptake Inhibitor, TCA: Tricyclic Antidepressant, MCI: Mild Cognitive Impairment.

Table 2. Impact of benzodiazepines and Z drugs on cognition

AUTHOR	YEAR	TYPE OF STUDY	SAMPLE SIZE	SETTING	PATIENT MORBIDITY	DRUG USED	CONTROL GROUP	DURATION OF FOLLOW-UP	COGNITIVE ASSESSMENT TOOLS	OUTCOME
Paternity et al	2001	Prospective cohort	$N = 1176$, 60–70 years	Electoral rolls of Nantes, France; community-dwelling individuals	Without dementia	BZD, categorized as episodic, recurrent, and chronic users	BZD non-users	Baseline, two years, four years	A battery of ten tests including MMSE, TMT-B, DSS, AVLT, FTT	A significant association between chronic use of BZD and global cognitive decline in the MMSE [OR] [95% confidence interval (CI)] = 1.9 [1.0–3.5]
Bierman et al	2007	Prospective cohort	$N = 2105$, $\geq$ 62 years of age	Netherlands, in 11 municipalities as part of Longitudinal Aging Study Amsterdam (LASA); community-dwelling individuals	Without dementia	BZD	BZD non-users	Nine years	MMSE, Coding task, RCPM, AVLT	BZD use worsened cognitive performances (decline in MMSE, $p < 0.001$), although effect sizes were very small (F2 <_0.01)
Gallacher et al	2012	Prospective cohort	$N = 1134$ men, born between 1920 and 1939	United Kingdom, part of Caerphilly prospective study in South Wales; community-dwelling older men.	Without dementia	BZD	BZD non-users	22 years, seen on five occasions	AH4, NART, MMSE, CAMCOG, four-choice reaction time task.	A significant association between regular use of BZD and the incidence of dementia (OR = 3.50, 95% CI 1.57–7.79, $p = 0.002$)
Van Vliet	2008	Prospective cohort	$N = 599$, ≥ 85 years	Netherlands, part of Leiden 85 plus study conducted in Leiden; community-dwelling individuals	Without dementia	BZD	BZD non-users	Five-year follow-up	MMSE, Stroop test, LDCT, PLT immediate and delayed	No association between BZD use and a decline in cognitive function, However, discontinued BZD users had a 4-point lower MMSE score in the year before discontinuation than continuing benzodiazepine users ($p = 0.004$)
Mura et al	2013	Prospective cohort	$N = 5195$, ≥ 65 years	France, part of three-city study, population-based study. community-dwelling individuals	Without dementia	BZD	BZD non-users	Seven years, assessed at baseline, two, four, and seven years	MMSE, Isaacs set test, BVRT, TMT A and B tests	No association was found between chronic use of BZDs and acceleration of cognitive decline ($p = 0.81$)

Table 2. Continued

AUTHOR	YEAR	TYPE OF STUDY	SAMPLE SIZE	SETTING	PATIENT MORBIDITY	DRUG USED	CONTROL GROUP	DURATION OF FOLLOW-UP	COGNITIVE ASSESSMENT TOOLS	OUTCOME
Bourgeois et al	2015	Prospective cohort	$N = 226$ subjects	Belgium, 10 nursing homes	Nursing home residents with MMSE score ≥ 18/30	BZD and z category users of at least 3 months duration	BZD non-users	One year	MMSE	Cognition decreased significantly over time in both groups, with no significant difference in MMSE between the groups ($p = 0.640$)
Gray et al	2016	Prospective cohort	$N = 3434$, ≥ 65 years	Integrated healthcare delivery system, Seattle, USA	Without dementia	BZD	BZD non-users	7.3 years, followed up every two years	CASI	Association found between regular BZD use and developing dementia with 1-year hazard ratios for developing dementia of 1.25 (95% confidence interval 1.03–1.51) for 1–30 TSDDs; 1.31 (1.00–1.71) for 31–120 TSDDs; and 1.07 (0.82–1.39) for ≥ 121 TSDDs.
Desplenter et al	2012	Prospective cohort	$N = 781$; ≥ 75 years (79.9)	Finland; city of Kuopio; community-dwelling and institutionalized individuals	Without dementia	Sedatives (BZDs and Z drugs)	Sedative free	Four years	MMSE	No significant association between sedative use and cognitive decline ($p = 0.051$)
Nafti et al	2019	Prospective cohort	$N = 5281$, ≥ 65 years,	Canada, multicenter from all provinces; community-dwelling and institutionalized individuals	Without dementia	BZD	BZD nonusers	10 years	100-point Modified Mini Mental State Examination (3MS)	Significant association was found between BZD use and the development of CIND (hazard ratio = 1.36; 95% CI = 1.08–1.72), but not with the development of dementia

BZD: Benzodiazepine, BVRT: Benton Visual Retention Test, TMT: Trail Making Test, CASI: Cognitive Abilities Screening Instrument, TSDD: Total Standardized Daily Doses, AVLT: Auditory Verbal Learning Test, MMSE: Mini-Mental State Examination, DSS: Digit Symbol Substitution test, FTT: Finger Tapping Test, RCPM: Ravens Colored Progressive Matrices, CAMCOG: Cambridge Cognitive assessment, NART: National Adult Reading Test, TSDD: Total Standardized Daily Doses, LDCT: Letter Digit Coding Test, PLT: Picture Learning Test, CIND: Cognitive Impairment Not Dementia.

Study outcomes

Among the eight studies conducted on participants without cognitive impairment at baseline, five noted the association between the use of benzodiazepines and the rate of cognitive decline. Gallacher *et al.* reported an increased incidence of dementia among benzodiazepine users as compared to nonusers, over a very long follow-up period of 22 years. Gray *et al.* also reported increased incidence of dementia with minimal exposure to benzodiazepines. Paterniti *et al.* noted significant cognitive decline among chronic benzodiazepine users as compared to nonusers, especially in tests of executive function, even after adjusting for depressive and anxiety symptoms, age, sex, and education. In another community-based study among 2,105 older adults, Bierman *et al.* noted a significant cognitive decline among regular users compared to nonusers of benzodiazepines. They also noted that cumulative use over longer durations corresponded to poorer performance on the MMSE, although the effect sizes were small. Lastly, a recent study conducted in a mixed community and nursing home setting with a 10-year follow-up period revealed a significant association between benzodiazepine use and the development of cognitive impairment not dementia (CIND), which is similar to MCI, but not with dementia (Nafti *et al.*, 2020).

Among studies that did not demonstrate cognitive decline with benzodiazepines, Mura *et al.* noted that users had poorer cognition at baseline as compared to nonusers. A similar finding was reported by Desplenter *et al.* Both these studies assessed baseline populations without dementia. A third study, which was carried out in a nursing home population with MMSE scores of 18 and above, did not find an association between rate of cognitive decline and benzodiazepine use (Bourgeois *et al.*, 2015). Van Vliet *et al.* noted that individuals who discontinued benzodiazepines had a four-point lower MMSE score in the year before discontinuation (van Vliet *et al.*, 2009) as compared to controls.

Antipsychotic studies

Study settings

Three studies (one RCT and two cohorts) examined the cognitive impact of antipsychotic medications in older adults (McShane *et al.*, 1997; Vigen *et al.*, 2011; Caballero *et al.*, 2006b). All three were carried out in English-speaking countries, and one study was multicenter (Vigen *et al.*, 2011). All the three were based in the community. The length of the follow-up period ranged from nine months to two years. Please refer to Table 3.

Participant details

All three studies included both male and female participants. All the studies included participants with dementia at baseline. Antipsychotics were prescribed for indications of psychosis and/or agitated or aggressive behavior in all three studies. Caballero *et al.* included only participants who were on cholinesterase inhibitors to assess the cognitive impact of atypical antipsychotics on this group.

Medication details

Vigen *et al.* studied the cognitive impact on patients on quetiapine, risperidone, or olanzapine. Caballero *et al.* noted that 82% of the patients were on quetiapine. McShane *et al.*, being an older study, reported that nearly all the participants were on typical antipsychotics including thioridazine, promazine, haloperidol, or chlorpromazine.

Study outcomes

Two of the three studies reported a significant cognitive decline in the antipsychotic medications group as compared to the control groups (McShane *et al.*, 1997; Caballero *et al.*, 2006b; Vigen *et al.*, 2011). The third study did not note any significant difference in the rate of cognitive decline between the antipsychotic and control groups (Caballero *et al.*, 2006b). Both atypical and typical antipsychotics were associated with cognitive decline (Vigen *et al.*, 2011; McShane *et al.*, 1997). In Vigen *et al.*, there was no significant difference in the rate of cognitive decline between the three atypical antipsychotics being studied. The study that did not report a significant cognitive decline (Caballero *et al.*, 2006b) had only participants on cholinesterase inhibitors in both study and control groups.

Mood stabilizer studies

Only one study (a double-blinded RCT) on the cognitive impact of mood stabilizers fulfilled the inclusion criteria (Fleisher *et al.*, 2011). The study was conducted in 46 centers in an English-speaking country (USA) and focused on participants with mild-to-moderate Alzheimer's' disease at baseline. The authors assessed the cognitive impact of divalproex sodium versus placebo over a 24-month follow-up period. Eighty-nine participants (46 placebo, 43 divalproex), including both men and women, were selected for a magnetic resonance imaging (MRI) substudy, and the scan was performed at baseline and at 12 months. In the MRI substudy, the divalproex group demonstrated a significantly greater decline in MMSE scores and greater overall brain and hippocampal volume loss in the first 12 months as compared to

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the placebo group (Fleisher et al., 2011). Please refer to Table 3.

Mixed medications studies

Study settings

Five studies (all cohorts) assessed the impact of a combination of psychotropic medication categories on cognition in the elderly (Allard, *et al.*, 2003; Berg and Dellasega, 1996; Oh *et al.*, 2021; Pirker-Kees, *et al.*, 2019; Shash *et al.*, 2016). One study was conducted in an English-speaking country (Oh *et al.*, 2021), and the rest were conducted in non-English-speaking countries in Europe. Three studies were multicenter and two were conducted with a population-based registry (Berg and Dellasega, 1996; Oh *et al.,* 2021). Four studies were based in the community, and one was in mixed community and institutional settings (Allard, *et al.*, 2003). The period of follow-up ranged from one to nine years. Please refer to Table 4.

Participant details

All five studies were conducted on both male and female participants. Two of the studies focused on participants with dementia (Oh *et al.*, 2021; Pirker-Kees, *et al.*, 2019), one focused on participants with varied cognitive abilities (Berg and Dellasega, 1996), and two on participants without dementia (Allard, *et al.*, 2003; Shash *et al.*, 2016).

Medication details

All five studies included participants on a range of psychotropic medications including antipsychotics, antidepressants, and sedative-hypnotics. Additionally, two studies included psychostimulant users (Allard, *et al.*, 2003; Shash *et al.*, 2016) and one included participants using nootropics (Shash *et al.*, 2016). Participants could be on either one or more of these drugs in three of the five studies but used only one category of drugs in the other two studies (Oh *et al.*, 2021; Pirker-Kees, *et al.*, 2019).

Study outcomes

Among the studies carried out on participants without dementia at baseline, Shash *et al.* reported increased incidence of dementia among participants using benzodiazepines with long half-life (≥ 20 hours). Allard *et al.* reported that cognitively unimpaired antidepressant users had significant improvement in measures of verbal and visual recall as compared to the control group, after adjusting for severity of depression.

Among the studies carried out among participants with dementia at baseline, Oh *et al.* noted that there was significant cognitive decline among users of atypical antipsychotics. The study also did not find any cognitive benefit from any drug category including antidepressants. Pirker-Kees *et al.* noted that while there was a significant cognitive decline among the entire study population (including controls), there was no significant decline in any specific medication group when compared to controls. Finally, in an older study, Berg *et al.* examined participants with varied cognitive states and noted that those on psychotropics as a category were more likely to have cognitive decline as compared to those who were not.

Discussion

This systematic review presents current evidence on the cognitive impact of multiple categories of psychotropic medications in older adults and adds to existing literature on this topic. Our study is the first to examine and compare the cognitive impact of various categories of psychotropic medications and a combination of these categories on older adults.

Impact of antidepressants

Participants without cognitive impairment at baseline appeared to be at increased risk of developing cognitive decline with use of antidepressants, as compared to those with preexisting cognitive impairment. While both SSRIs and TCAs were associated with cognitive decline in this population, there was considerable evidence that paroxetine was the SSRI most associated with cognitive decline. The cognitive decline caused by TCAs and paroxetine could be easily explained by their anticholinergic properties. Use of these categories of antidepressants among older adults would clearly be cognitively deleterious, as supported by extensive previous research (Attoh-Mensah *et al.*, 2020; Mate *et al.*, 2022).

It is challenging to understand the relative impact of antidepressants and depression on cognition, as cognitive decline could be explained by either the medications or the underlying depression itself, with research indicating that depression is an independent risk factor for the development of dementia (Livingston *et al.*, 2020). By this logic, successful treatment of depression should improve cognition or prevent cognitive decline in older adults with depression. However, evidence has been conflicting with increased incidence of dementia noted among antidepressant users, regardless of category of the antidepressant used (Bartels *et al.*, 2020; Brown, *et al.*, 2020). In our study, Wang *et al.* and Goveas *et al.* noted that depressed antidepressant users without cognitive impairment at baseline had worse cognitive decline than depressed nonusers at follow-

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Table 3. Impact of antipsychotics and mood stabilizers on cognition

Author	Year	Type of study	Sample size	Setting	Participant morbidity	Drug used	Control group	Duration of follow-up	Assessment tools	Outcome
McShane et al	1997	Prospective cohort	$N = 71$, mean age = 72.6 years	United Kingdom; community-dwelling individuals in Oxfordshire	With dementia	Antipsychotics	Antipsychotic free	Two years, with interviews every four months and necropsy follow-up	Expanded MMSE	The mean decline in cognitive score among the antipsychotic group ($n = 16$) was twice that of those in the non-user group ($p = 0.002$). There was no correlation between the neuroleptic dose and the cognitive decline rate ($r = 0.19$, $p = 0.4$)
Caballero et al	2006	Retrospective cohort	$N = 92$, mean age = 72.4 years	Outpatients at the Department of Neurology, Columbus, Ohio, USA	Mild-to-severe definite or probable Alzheimer's disease on cholinesterase inhibitors	Atypical antipsychotics	Atypical antipsychotic free	Six months or more, the mean follow-up period was 421 days	MMSE	No significant difference between the groups in the rate of decline on MMSE ($p =$ not significant)
Vigen et al	2011	RCT	$N = 421$, mean age = 77.6 years	Outpatients at 42 sites in the USA	With Alzheimer's disease with psychosis or agitated behavior	Atypical antipsychotic medications – olanzapine, quetiapine, or risperidone	Placebo, excluded if taking antidepressants or anticonvulsants for mood stabilization	36 weeks, outcomes obtained at baseline, 12, 24, and 36 weeks	MMSE, ADAS-cog, finger tapping, trails A, dot tests	Significant association found between atypical antipsychotic use and cognitive decline on MMSE ($p = 0.004$)
Fleisher et al	2011	Double-blind RCT	89 participants (46 placebo, 43 divalproex) aged 55 years and above	Multicenter in 19 sites in USA	Mild-to- moderate Alzheimer's disease without behavioral symptoms and MMSE scores of 12–20	Divalproex sodium	Placebo	24 months, with six monthly cognitive assessments. MRI scans were done at baseline and 12 months	ADAS – COG), CDR-SB MMSE	MMSE scores showed a decline with divalproex till 12 months ($p = 0.037$), but not thereafter. The MRI subgroup on divalproex showed accelerated hippocampal and brain volume loss as compared to the placebo group ($p < 0.001$)

ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive subscale, MMSE: Mini-Mental State Examination, CDR-SB: Clinical Dementia Rating Sum of Boxes score, RCT: Randomized Controlled Trial, MRI: Magnetic Resonance Imaging.

Table 4. Impact of mixed or multiple drug categories on cognition

AUTHOR	YEAR	TYPE OF STUDY	SAMPLE SIZE (N) AND AGE (MEAN)	SETTING	PARTICIPANT MORBIDITY	DRUG USED	CONTROL GROUP	DURATION OF FOLLOW-UP	COGNITIVE ASSESSMENT TOOLS	OUTCOME
Shash et al	2016	Prospective cohort study	$N = 8240$; age = ≥ 65 years (74.7)	France; multi-center (three cities); community-dwelling individuals	Without dementia	BZDs, antipsychotics, anxiolytics, hypnotics, sedatives, antidepressants, psychostimulants, nootropics, or a combination of these drugs	Psychotropic free	Median follow-up of eight years	MMSE and Isaacs set test	The psychotropic group had an increased risk of dementia (HR = 1.47; 1.16–1.86) as compared to the controls. Users of long half-life BZDs had a marked increased risk of dementia (HR = 1.62; 1.11–2.37)
Allard et al	2003	Prospective cohort study, part of Eugeria longitudinal study of cerebral aging	$N = 372$; mean age 75.7 years	France; community-dwelling and institutionalized individuals	Without dementia	Anxiolytics, hypnotics, antidepressants, neuroleptics, psychostimulants, and a mixed group	Psychotropic free	Three years, at yearly intervals	Computer-based cognitive examination	Significant positive effects were seen in antidepressant users in tests of verbal recall ($p = 0.002$) and visual recall ($p = 0.025$). No effect was found for BZDs
Berg et al	1996	Prospective cohort and cross-sectional study	$N = 743$; age = 70 years	Population register in Sweden, community-dwelling individuals	Varied cognitive abilities	Neuroleptics, antidepressants, anxiolytics, sedatives or hypnotics, and a combination of these drugs	Psychotropic free	Nine years. The same cohort was assessed at 70, 75, and 79 years of age	Thurstone Memory Test, Digit span test from WAIS	The longitudinal analysis demonstrated a decline in multiple cognitive domains in the psychotropic group ($p < 0.01$)
Oh et al	2021	Cohort	$N = 8034$, mean age = 75.5 years	USA, multicenter, community-dwelling individuals using NACC database	With Alzheimer's disease	Antipsychotics, antidepressants, and BZDs	Participants on a medication class were matched with individuals not using that class of drugs	2.9–3.3 years	MMSE	Atypical antipsychotic use was significantly associated with a greater decline in the MMSE ($p = 0$ .005)
Pirker-Kees et al	2019	Cohort	$N = 309$, mean age 76 years	Austria, multicenter, community-dwelling individuals	With dementia	Monotherapy with SSRIs, trazodone, atypical antipsychotics, BZDs	Psychotropic free	One year	MMSE	No significant association was found between change in MMSE scores with use of any psychotropic medication (p = not significant)

MMSE: Mini-Mental State Examination, BZD: Benzodiazepine, SSRI: Selective Serotonin Reuptake Inhibitor, WAIS: Wechsler Adult Intelligence Scale, NACC: National Alzheimer's Coordinating Center.

up, indicating that the decline at follow-up was likely antidepressant related. This finding applied to SSRI as well as non-SSRI antidepressant users. However, it was not mentioned if this SSRI-related cognitive decline was driven by an agent with anticholinergic property such as paroxetine.

There appears to be relatively less cognitive impact of antidepressants among participants with preexisting cognitive decline. We could speculate that this is due to the possibly small cognitive impact of antidepressants, which might not be significant for participants with considerable deficits at baseline. However, this finding is to be examined with caution as most of the studies included in our review were conducted among participants without cognitive impairment at baseline, with relatively less representation of those with MCI or dementia at baseline. Although slowing of cognitive decline with long-term SSRI use among nondepressed participants with MCI was reported by Bartels *et al.*, we were not able to reach any conclusion on cognitive protective properties of these agents in this population due to the limited number of studies on this topic fulfilling our inclusion criterion. The improvement of cognitive deficits among sleep-deprived participants with cognitive impairment at baseline with the use of trazodone could be explained by its slow-wave sleep-enhancing effect. Further rigorous research, especially RCTs to assess the cognitive impact of non-paroxetine SSRIs and trazodone among participants with and without cognitive impairment at baseline, with the use of rating scales to measure the severity of depression at baseline and at the time of follow-up is required.

Impact of benzodiazepines

Most of the studies conducted among participants without cognitive impairment at baseline reported a significant cognitive decline associated with the use of benzodiazepines. However, the size of the impact was small in several studies. Factors associated with cognitive decline include regular use, longer duration of use, and use of longer acting agents. This finding is understandable, based on the increased cumulative burden these patterns of use might cause. However, no clear consensus was noted between the dose of the agents with cognitive decline, thus making it less likely that the decline could purely be explained by the anticholinergic properties of the drug. One study reported cognitive decline with even small doses of benzodiazepine use, potentially indicating treatment of prodromal symptoms of dementia with benzodiazepines (Gray *et al.*, 2016). It is worth noting that eight of the nine studies were among participants without cognitive impairment at baseline. It is possible that benzodiazepines were used more in participants with early undiagnosed dementia to treat psychological symptoms. It is therefore difficult to rule out reverse causality, especially as all the included studies were observational in nature. However, certain studies like Gallacher *et al.* had very long follow-up periods, limiting the impact of reverse causality. The mechanism through which benzodiazepines cause cognitive change in the brain is unclear and was not addressed in detail in any of the studies we included.

It is interesting to note that of the three studies that did not report cognitive decline with the use of benzodiazepines among participants without cognitive impairment at baseline, one had a relatively small sample size of 226 participants and a shorter follow-up period of one year, as compared to the other studies that were included (Bourgeois *et al.*, 2015). Another study noted that participants had a four-point lower MMSE score before discontinuation, indicating a phenomenon described by the authors as "depletion of susceptibles," indicating that the declining cognitive function prompted treating physicians to stop prescribing benzodiazepines to these participants (van Vliet *et al.*, 2009).

There were limited studies looking into the cognitive impact of benzodiazepines among participants with cognitive impairment at baseline. This is understandable given the increasing awareness of the harms of their use in this population, including cognitive decline, falls, and fractures (Mathieu *et al.*, 2021; Pariente *et al.*, 2008). Given this, there will be serious ethical concerns about carrying out RCTs to determine the cognitive impact of benzodiazepines among older adults. We may postulate that had these participants continued to receive benzodiazepines, we would see a stronger relationship between their use and cognitive decline. It is possible that the other studies might have nonsignificant results due to this effect. Future studies reporting the cognitive performance of participants prior to discontinuing benzodiazepine use would help better understand the relative contribution of this effect.

Based on our findings and prior research, it is possible to draw a conclusion that cumulative use of benzodiazepines, through regular and long-term use, and the use of longer acting agents iare linked with cognitive impairment among older adults without cognitive impairment at baseline, although the effect size is small in the included studies.

Impact of antipsychotics

Most of the included studies reported a significant cognitive decline with the use of antipsychotic medications among older adults, ranging from twice that in control groups or equal to one year of degenerative disease (McShane *et al.*, 1997; Vigen

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et al., 2011). This is in keeping with prior research on this area (Kim *et al.*, 2021). This is in contrast with the small size of cognitive impact reported in the benzodiazepine studies. Both typical and atypical agents were associated with cognitive decline. No difference in the rate of decline was noted in CATIE-AD among quetiapine, risperidone, or olanzapine. Based on this, it is unlikely that anticholinergic side effect could explain the cognitive decline, as these agents have varied anticholinergic properties. All the studies included were conducted on participants with preexisting cognitive decline and behavioral and psychological symptoms of dementia with clinical indication for the use of antipsychotic medications. Like our findings in the benzodiazepine and antidepressant categories indicate, we could speculate that the cognitive impact would be worse if antipsychotic agents were prescribed to older adults without cognitive impairment. Of note, the only study that did not demonstrate cognitive decline with antipsychotic use included only participants on cholinesterase inhibitors (Caballero *et al.*, 2006b). It is possible to speculate that cholinesterase inhibitors could protect from the deleterious impact of antipsychotics on cognition, and this could be a very interesting area for future research.

Impact of mood stabilizers

The one study that fulfilled our search criterion and was included in the review clearly indicated the deleterious impact of divalproex on cognition among older adults with dementia. Brain volume loss in the first 12 months of use was noted, with the authors speculating if this was explained by reversible encephalopathy due to the drug. As MRI scans were not repeated at 24 months, it is not clear if there was a reversal of brain volume loss over time. The study concluded that use of divalproex in participants with dementia could not be recommended given these concerning findings. While there is evidence to suggest a positive cognitive impact of lithium on patients with Alzheimer's diseases, studies assessing this relationship could not be included in our review as they did not fulfill our inclusion criterion of participants being 55 years and over (Chen *et al.*, 2022; Matsunaga *et al.*, 2015).

Impact of combination of psychotropic drugs

This was a heterogenous group of studies, with varied intake populations and drug categories used making it difficult to reach a consensus. There was a significant cognitive decline reported with use of atypical antipsychotics and benzodiazepines, which agrees with previous studies included in our review. An increased incidence of dementia was reported among nondepressed cognitively intact participants on longer acting benzodiazepines, which agrees with our previous findings (Shash *et al.*, 2016). This indicates that the cognitive impact was likely due to the psychotropic use and that the agents were not given for psychological symptoms that could be a prodrome of dementia. Participants on a combination of benzodiazepines and other psychotropics and psychotropics as a group had an increased incidence of dementia, likely indicating the combined impact of the drug categories on cognition (Berg and Dellasega, 1996; Shash *et al.*, 2016). This agrees with previous research on this area (Borda *et al.*, 2021).

However, the findings from some studies in this group should be interpreted with caution as the number of participants in various drug categories was quite small, limiting the power of the study. Allard *et al.*, included only 20 participants on antidepressants at baseline. Similarly, Pirker-Kees *et al.* had small medication groups with 22 participants on SSRIs, eight on trazodone, and 18 on either benzodiazepines or atypical antipsychotics. While increased cognitive decline with psychotropic drug use was reported, the study in question had significant limitations (Berg and Dellasega, 1996). There were no details provided on the medications used, and the findings were not adjusted for severity of psychiatric illness. Therefore, the impact of the underlying psychiatric illness and reverse causation could not be ruled out conclusively.

Strengths and limitations of the study

Our study has several strengths. We only included studies that used validated cognitive scales to quantify cognitive changes. We restricted our search to include studies that have control groups, a follow-up period of at least six months, and relatively large sample sizes. The systematic review was also restricted to include only higher levels of evidence such as RCTs and cohort studies. We did not limit the search based on years since publication, study settings, or language parameters, adding to the robustness of the study.

Our review has certain limitations that we would like to acknowledge. Most of the studies that were included assessed the cognitive impact of antidepressants or benzodiazepines with relatively few evaluating the impact of mood stabilizers or antipsychotic medications. Further, most of the studies included were observational in nature, and there were only two RCTs that fulfilled our criterion. While we attempted to examine if the anticholinergic effect could explain the negative cognitive impact of psychotropic medications, it was difficult to comment on this as many studies did not

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specify the individual drugs used in any psychotropic class. The mechanisms through which the cognitive impact was caused and was not explored in most studies. Given the use of psychotropic medications for behavioral and psychological symptoms of early dementia, we also cannot rule out reverse causality, especially in observational studies with shorter follow-up periods. However, conducting RCTs on the cognitive impact of antidepressants versus placebos among depressed participants would raise ethical concerns. Finally, the findings of a systematic review are dependent on the quality of methodology of the constituent studies. We attempted to mitigate this risk by including only studies that present a higher level of evidence such as cohort studies and RCTs.

Clinical implications

It is imperative for clinicians prescribing psychotropic medications to older adults to be informed about the cognitive impact of psychotropic medications, especially as many of these medications are continued for longer periods of time. Older adults on regular use of longer acting benzodiazepines, antipsychotics, antidepressants with anticholinergic properties, or psychotropic combinations are especially vulnerable to the possibility of cognitive decline, even if they had no cognitive impairment at baseline. The use of such agents should be accompanied with caution and after clinical deliberation. There is potential to prevent such decline by assessing cognition prior to starting these psychotropics and at periodic intervals thereafter.

Conclusions and future directions

Our study identified an association between the cumulative use of benzodiazepines, antidepressants with anticholinergic properties, and antipsychotics with cognitive decline among older adults. In addition, we noted that participants without cognitive impairment at baseline appeared more sensitive to the deleterious impact of antidepressants and benzodiazepines as compared to those with pre-existing dementia. There is paucity of RCTs on the impact of psychotropic medications on the cognition of older adults with large sample sizes, long follow-up periods, and use of cognitive measures. Further, much of the available literature is on the cognitive impact of benzodiazepines or antidepressants among older adults. There is a need for future rigorous research on the cognitive impact of other psychotropic agents including mood stabilizers and antipsychotic medications among cognitively unimpaired older adults with long follow-up periods and to examine the molecular pathways through which these medications cause cognitive decline.

Conflict of interest

The authors have no conflicts of interest to declare. All co-authors have reviewed and agree with the contents of the manuscript.

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Description of authors' roles

S. Chandramouleeshwaran designed the study, collaborated the search strategy, reviewed the data, extracted the data, and wrote the manuscript. W.U. Khan collaborated with study design, reviewed the data, assisted with data extraction, and reviewed the manuscript. F. Inglis designed and implemented the search strategy, assisted with writing the paper and reviewed the manuscript. T.K. Rajji designed the study, reviewed the data, and edited the manuscript.

Supplementary material

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