Basic and Clinical
NEUROSCIENCE

January & February 2025, Vol 16, No. 1

Research Paper

Effect of Anticholinergic Medications on the Risk of Dementia: A Systematic Review and Meta-analysis Protocol

Elham Maraghi[1], Ali Reza Safarpour[2], Maryam Hajmohammadi[3], Ali Akbar Oroojan[4], Amal Saki Malehi[5], Hadis Ashrafizadeh[5*]

1. Department of Biostatistics and Epidemiology, School of Health, Ahvaz Jundishapur University of Medical sciences, Ahvaz, Iran.
2. Gastroenterohepatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
3. Student Research Committee, Department of Biostatistics and Epidemiology, School of Health, Ahvaz Jundishapur University of Medical sciences, Ahvaz, Iran.
4. Student Research Committee, Department of Physiology, Faculty of Medicine, Dezful University of Medical Sciences, Dezful, Iran.
5. Faculty of Nursing, School of Nursing, Dezful University of Medical Sciences, Dezful, Iran.

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Citation Maraghi, E., Safarpour, A. R., Hajmohammadi, M., Oroojan, A. A., Saki Malehi, A., & Ashrafizadeh, H. (2025). Effect of Anticholinergic Medications on the Risk of Dementia: A Systematic Review and Meta-analysis Protocol. *Basic and Clinical Neuroscience, 16*(1), 55-64. http://dx.doi.org/10.32598/bcn.2022.3823.1

doi http://dx.doi.org/10.32598/bcn.2022.3823.1

Article info:
Received: 28 Oct 2021
First Revision: 24 Jan 2022
Accepted: 07 Feb 2022
Available Online: 01 Jan 2025

Keywords:
Anticholinergic drug, Cholinergic antagonist, Dementia, Alzheimer, Systematic review, Meta-analysis

ABSTRACT

Introduction: The most frequent dementia is senile dementia or Alzheimer disease. Meanwhile, anticholinergic drugs can potentially modify the risk factors. As different studies have achieved dissimilar results and the clinical findings of these interventions have not been conclusive, the objective of this research will be to evaluate the effect of anticholinergic drugs on the risk of dementia.

Methods: This systematic review and meta-analysis with no language limitation will search WoS, EMBASE, and MEDLINE via PubMed, Scopus, ProQuest electronic databases, and Grey Literature between December 15, 1988, and December 15, 2021. Our search strategy with suitability criteria covers cohort, case-control, nested case-control, randomized, and non-randomized clinical trial studies evaluating the effect of anticholinergic drugs on the risk of dementia. Two authors will independently implement the selection phase, data extraction, and quality assessment. The reviewers will evaluate the risk of bias using the Newcastle-Ottawa, Cochrane risk of bias tool and ROBINS-I (risk of bias in non-randomized studies - of interventions) quality assessment scale. We will conduct a meta-analysis with a random or fixed effect model according to the severity of methodological heterogeneity. The results will be presented via the forest plot for the final studies' data composition, demonstrating the separated and combined frequency and their corresponding 95% CIs, summary tables, and narrative summaries.

Conclusion: The results of different studies in this field are various. This study's findings and other studies will help physicians and other health professionals before prescribing these drugs. Older people, especially those with polypharmacy, should be carefully assessed for the risk of dementia, Alzheimer or a variety of cognitive disorders.

*** Corresponding Author:**
Hadis Ashrafizadeh
Address: *Faculty of Nursing, School of Nursing, Dezful University of Medical Sciences, Dezful, Iran.*
Tel: *+98 (933) 5047127*
E-mail: *Ashrafizadeh.h1993@gmail.com*

Highlights

- This systematic review and meta-analysis will carefully evaluate the association between anticholinergic drug use and the occurrence of dementia in older adults.
- No language restriction will be applied.
- Three biostatisticians will review the information included in the studies.
- Risk assessment will be done using two commonly used tools.
- Imprecision in the pooled effect estimate due to small sample sizes in some studies should be considered a limitation.

Plain Language Summary

Due to the increase in the number of aged population worldwide, the prevalence of debilitating diseases such as dementia has significantly increased. One risk factor for dementia is the use of anticholinergic drugs. They have short-term cognitive adverse effects. Due to the widespread use of anticholinergics, many studies have been conducted to investigate the relationship between the use of anticholinergic drugs and the risk of dementia. This is a study protocol for systematic review and meta-analysis of these studies. The findings can help physicians and other health professionals to gain information before prescribing these drugs. Older people, especially those with polypharmacy, should be carefully assessed for the risk of dementia, Alzheimer's disease, or a variety of cognitive disorders.

1. Introduction

In recent years, the growing rate of the world's older population (1.9%) has significantly exceeded the ascending rate of the world's whole population (1.2%). By 2020, the population of individuals over 60 is expected to reach 2 billion (WHO, 2014), and that of people over 65 will reach 1.5 billion. In 2030-2050, the aging population will increase 3.5 times faster than the total population growth (2.8 % vs 0.8 %, respectively). Further, with the rising number of older people in the world, the number of people with dementia is expected to triple from 50 million by 2030 to 152 million by 2050 (McNicoll, 2002). With the increase in the number of aging population worldwide, debilitating diseases significantly increase (Farhadi et al., 2018).

One of the most common disorders observed in older people is the cognitive disorder dementia, which is associated with severe and progressive disability (Craik & Salthouse, 2011; Dixon, 2004). Different types of dementia comprise Alzheimer disease, vascular dementia, dementia with Lewy bodies, Parkinson disease dementia, mixed dementia, front temporal dementia, Huntington's disease, and Creutzfeldt-Jakob disease (Chandra et al., 1986). The most common kind of dementia is senile dementia (Colombia, 2016). It is a degenerative cerebrovascular disorder that aggravates over time (Gaugler et al., 2019). The number of prevalent dementia cases between 1990 and 2016 rose by 117% from 20.2 million in 1990 to 43.8 million. Generally, every three seconds, one person in the world is affected by the disease. Globally, 50 million people live with Alzheimer disease, and approximately 60% of them live in low- or middle-income countries. In addition, 10 million new cases are diagnosed annually. It has been estimated that the proportion of people aged 60 years and over with Alzheimer disease, at a certain time, is 5%-8% of the general population (Brookmeyer et al., 2002; Cummings & Cole, 2002; Flaxman et al., 2015; Iran, 2018; WHO, 2019). About 35% of risk factors of dementia cases are amendable, including high blood pressure, depression, hearing loss, smoking, and diabetes (Livingston et al., 2017). Another risk factor for dementia is the use of anticholinergic drugs (Coupland et al., 2019). Anticholinergic medicines have short-term cognitive adverse effects, but it is uncertain whether long-term use of these drugs is associated with an increased risk of dementia (Coupland et al., 2019). Some anticholinergic drugs work by blocking the effect of acetylcholine on muscarinic receptors within specific organ systems (e.g. gastrointestinal antispasmodics, bladder antimuscarinics, and anti-Parkinson agents) (Fox et al., 2011; Fox et al., 2014; Gray et al., 2015).

The brain's cholinergic system plays a major role in current research into natural cognition and age-related cognitive decline, including dementia, such as Alzheimer disease. The cholinergic hypothesis of Alzheimer disease focuses on the progressive loss of the limbic and neocortical cholinergic nerves. Neurofibrillary degeneration in the forebrain is believed to be the main cause of dysfunction and death of forebrain cholinergic neurons, leading to extensive presynaptic cholinergic nerve severance. Cholinesterase inhibitors increase the availability of acetylcholine at brain synapses and are one of the few drug therapies clinically helpful in treating Alzheimer dementia. Therefore, they confirm that the cholinergic system is an important therapeutic target in this disease (Hampel et al., 2018).

Due to the widespread use of anticholinergics, many studies have been conducted to investigate the relationship between the use of anticholinergic medications and the chance of dementia. Bhattacharya et al. (2011) demonstrated that anticholinergic drugs, though often used in the older population, are associated with cognitive disorders and are a significant concern for patients with dementia. Richardson et al. (2018) showed a strong relationship between some types of anticholinergic medications and the onset of early signs of dementia in the future. Richardson et al. (2015) showed that the use of anticholinergic drugs is related to dementia in men but was not observed in women. Coupland et al. (2019) revealed that concomitant use of more than one potent anticholinergic drug increased the risk of dementia. These results emphasize the need to reduce the use of anticholinergic medications in older people.

Dmochowski et al. (2021) showed that the use of anticholinergic drugs to control an overactive bladder for 3 months increased the risk of dementia by an average of 46% versus non-use (Dmochowski et al., 2021). In addition, the results of a meta-analysis conducted in November 2020 by Pieper et al. showed that the use of anticholinergic drugs increases the risk of dementia. However, no causal link can be deduced as the studies were associated with a significant risk of bias (Dmochowski et al., 2021). Nonetheless, researchers plan to increase the comparative advantages of the present study to minimize bias. Since different studies, such as observational and meta-analysis studies, have achieved different results and the clinical results of these interventions have not been conclusive, finding a definitive result to prevent side effects from polypharmacy in older people is a priority worldwide. Based on what was discussed, this study will be performed to calculate the integrated estimate of dementia risk in patients taking different types of anticholinergic drugs and finding possible sources of heterogeneity and considering randomized clinical trials (RCTs) and non-randomized clinical trials as acceptable study type.

2. Study Aims

Preliminary objective

The preliminary outcome of this research includes assessing the effect of anticholinergic medications on the risk of dementia.

Secondary objectives

The secondary objectives will be as follows:

Estimating the effect of anticholinergic medications on the risk of dementia and Alzheimer by age group,

Estimating the effect of anticholinergic medications on the risk of dementia and Alzheimer by gender,

Estimating the effect of anticholinergic medications on the risk of dementia and Alzheimer by ethnicity,

Estimating the effect of anticholinergic medications on the risk of dementia and Alzheimer by type of anticholinergic drug,

Estimating the effect of anticholinergic medications on the risk of dementia and Alzheimer by duration of drug use,

Estimating the effect of anticholinergic medications on the risk of dementia and Alzheimer by the different study populations and

Assessing potential heterogeneity in the effect of anticholinergic medications on the risk of dementia and Alzheimer and finding its possible sources.

3. Materials and Methods

Study design

This protocol will be presented according to the precedent preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 and a meta-analysis of observational studies in epidemiology guidelines (MOOSE) (Brooke et al., 2021).

In addition, this protocol is registered in the prospective submission and publication of key information about the design and conduct of a systematic review (PROSPRO) (Code: CRD42020219612).

Suitability criteria of primary studies

Inclusion and exclusion criteria

Type of study

This study will capture prospective and retrospective observational articles (cohort study, case-control, nested case-control), RCTs, and non-randomized clinical trials that estimate the effect of anticholinergic drugs on the incidence of dementia and Alzheimer. On the other hand, review articles, letters to the editor, case series, cross-sectional, short surveys, case reports, and books will not be included. No limitation will be applied on language and sample size for the preliminary studies to be included.

Participants' type

In observational studies (cohort study, case-control, nested case-control), individuals in the case group include all patients diagnosed with dementia or Alzheimer disease during follow-up after prescription of anticholinergic drugs with any age group, gender, race, and ethnicity. All studies evaluating individuals placed as controls for the case group after matching will be included. In RCTs, studies containing a comparison group that did not have any use of anticholinergic drugs will be considered for inclusion.

Disease outcomes

In this study, the definition of dementia includes an acquired organic mental disorder with a loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive and initially spares the level of consciousness. Moreover, the ICD-10 diagnosis codes (F01-F99, F01-F09, and F03) are approved for dementia. Also, the definition of Alzheimer includes a degenerative disease of the brain characterized by the insidious onset of dementia. Impairment of memory, judgment, attention span, and problem-solving skills are followed by severe apraxia and a global loss of cognitive abilities. The condition primarily occurs after age 60 and is marked pathologically by severe cortical atrophy and the triad of senile plaques, neurofibrillary tangles, and neuropil threads (Adams et al., 1997). Moreover, the ICD-10 diagnosis codes (F01-G00-G99 and G30-G30-9) are approved for Alzheimer disease.

Exposure

The preliminary exposure was to all standardized daily doses of anticholinergic medications determined in years prior to the date of diagnosis of dementia or equivalent date in matched controls (index date).

Search strategy and sources of literature

Strategy of search

With no language limitation, this systematic review and meta-analysis will search in the Web of Science, MEDLINE via PubMed, EMBASE, Scopus, ProQuest, and Google Scholar electronic databases between December 15, 1988, and December 15, 2021. Theses, conference papers, and meeting abstracts will be searched in International Statistical Institute (ISI), Scopus, and ProQuest databases. For finding the synonyms of search components (anticholinergic drug, cognitive disorder, dementia, Alzheimer), systems of thesaurus containing MeSH, Emtree, and free text method, the experts' opinion, as well as relevant papers and abstracts will be applied. The online supplement will provide details on how to search the PubMed database (Table 1). If we come across studies from other languages such as Portuguese, Chinese, Japanese, etc. we will use the Google translation service and an official translator familiar with that language for more assurance.

Reference lists and key journals of relevant studies

A manual search will be performed on the key journals. Based on the analysis of the search results in the databases, the journal selection phase will be done. Based on the research eligibility criteria, this search will be managed to detect the journals presented as the most significant storage of sources available on the paper topic. Also, a manual search will be done in the references list of the last papers that would become candidates for quality assessment. These studies will be combined with the last articles' list if we face articles in the former review studies and systematic review studies that have been missed in the prior search.

Grey literature

We will research electronic databases, including ProQuest and Scopus, to find a thesis related to the subject of the study. We will also contact experts in the subject area. ROBINS-I (Risk of Bias in non-randomized studies-of interventions) and NOS (Newcastle-Ottawa scale) tools will be used to evaluate the quality of the thesis searched in gray literature according to its methodology. In addition, electronic databases and expert information will be used to obtain conference papers and proceedings. This search will be done manually. A third-person expert contact will be made with the corresponding author(s) to access the full text of conference papers. In addition, when unpublished works are retrieved in our search, an email will be sent to the corresponding author(s) to determine whether the work has been subsequently published. The study will be excluded if there is no response from the corresponding author(s) after three emails.

Contacting expert persons

In this study, we will contact experts and ask them to send us any unpublished studies and dissertations related to the article's objectives. Also, we will ask them to introduce conferences relevant to the subject of this research. Further, manual research of the electronic databases will be done.

Screening and selection

Initially, studies retrieved from the search in the electronic database will be transferred to EndNote Software version 7, and duplicate articles will be removed from the software (EndNote library). Then, during the screening phase, two researchers (Hadis Ashrafizadeh and Maryam Hajmohammadi) will independently evaluate all of the primary studies based on the title and abstract, and two researchers will check for all studies that match the search strategy to select eligible studies based on the inclusion criteria. The selected articles will be categorized into three groups: Related, unrelated, and uncertain. Articles categorized as unrelated by two researchers will be excluded from the study. Afterward, in the selection phase, two researchers (Hadis Ashrafizadeh and Maryam Hajmohammadi) will independently assess the full texts of the remaining articles. Each researcher will provide a list of selected articles, and the two lists will be compared. Any discrepancies between researchers will be resolved by consensus, and in case no agreement is attained, a third expert person will act as a reviewer (Ali Akbar Oroojan or Ali Reza Safarpour). The agreement between the two researchers will be evaluated, and the result will be reported using the Kappa coefficient and overall agreement.

Risk of bias assessment

Two reviewers (Hadis Ashrafizadeh and Maryam Hajmohammadi) will independently assess the risk of bias as well as methodological quality of preliminary studies according to NOS for retrospective and prospective studies (for case-control, nested case-control, and cohort studies), Cochrane risk of bias tool for randomized controlled trials will be used for risk of bias assessment of RCTs and ROBINS-I (Higgins, 2011; Stang, 2010; Sterne et al., 2016). The NOS scale has 8 parts covering selection, comparability, and outcome (Stang, 2010). ROBINS-I scale has 7 sections of bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, bias in selection of the reported result (Sterne et al., 2016). Other tools will also be used to increase quality. Cochrane risk of bias tool has 7 sections: Random sequence generation, allocation concealment, selective reporting, and other biases such as bias due to problems not covered elsewhere in the table, blinding of participating and personnel, blinding of outcome assessment, incomplete outcome data (Higgins et al., 2011). Any discrepancies between researchers will be resolved by consensus, and in case no agreement is attained, a third expert person will act as a reviewer (Ali Reza Safarpour).

Data extraction

Two researchers (Hadis Ashrafizadeh and Maryam Hajmohammadi) will separately extract data using a researcher-made data extraction form. First, an article will be piloted with a data extraction form, which will then be used for other articles. Each researcher presents the information extracted from an article in the data extraction form, where the two forms will be compared. Any discrepancies between two reviewers will be resolved by consensus; otherwise, a third expert will act as a reviewer (Ali Akbar Oroojan). Then, the agreement between the two researchers will be evaluated. The subsequent data will be elicited from the selected articles: Name of first author, journal name, year of publication, country in which the study was done, design of study, prospective or retrospective design, target population, method of sampling, the sample size in the two groups, course of follow-up (length of study), and items relevant to study quality assessment (the score of every segment and the general score of the study quality). The participants' characteristics include age (age groups), gender, ethnicity, smoking, alcohol consumption, history of heart disease, stroke, high blood sugar and hyperten-

Table 1. The search strategy used in PubMed/MEDLINE

Number	Search Term
1	((Antagonists[tiab] AND cholinergic[tiab]) OR "cholinergic antagonist"[tiab] OR cholinergic-blocking agents[tiab] OR (agents[tiab] AND cholinergic-blocking[tiab]) OR "cholinergic blocking agents"[tiab] OR cholinolytic[tiab] OR "acetylcholine antagonists"[tiab] OR (antagonists[tiab] AND acetylcholine[tiab]) OR "cholinergic receptor Antagonists"[tiab] OR (antagonists[tiab] AND "cholinergic receptor"[tiab]) OR ("receptor antagonists"[tiab] AND cholinergic[tiab]) OR "anticholinergic agents"[tiab] OR (agents[tiab] AND anticholinergic[tiab]) OR anticholinergic OR anti-cholinergic*[tiab] OR "anti cholinergic"[tiab] OR antimuscarinic*[tiab] OR muscarinic antagonist*[tiab] OR anti-muscarinic[tiab] "atropinic agent"[tiab] OR "atropinic drug"[tiab] OR atropinol[tiab])
2	("Alzheimer's disease"[tiab] OR (dementia[tiab] AND senile[tiab]) OR "senile dementia"[tiab] OR (dementia[tiab] AND "alzheimer type"[tiab]) OR "alzheimer type dementia"[tiab] OR "alzheimer-type dementia"[tiab] OR ATD[tiab] OR (dementia[tiab] AND "alzheimer-type"[tiab]) OR (dementia[tiab] AND "primary senile degenerative"[tiab]) OR "alzheimer sclerosis"[tiab] OR (sclerosis[tiab] AND alzheimer[tiab]) OR "alzheimer syndrome"[tiab] OR "alzheimer dementia"[tiab] OR (dementia[tiab] AND alzheimer[tiab]) OR ("senile dementia"[tiab] AND "alzheimer type"[tiab]) OR ("senile dementia"[tiab] AND "acute confusional"[tiab]) OR (dementia[tiab] AND presenile[tiab]) OR ("alzheimer disease"[tiab] AND "late onset"[tiab]) OR ("alzheimer's disease"[tiab] AND "focal onset"[tiab]) OR fad[tiab] OR ("alzheimer disease"[tiab] AND familial[tiab]) OR ("alzheimer disease"[tiab] AND "early onset"[tiab]) OR "presenile alzheimer dementia"[tiab] OR "cognitive disorder"[tiab])
3	1988/12/15:2021/12/15[dp]
4	1 AND 2 AND 3

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sion, type of anticholinergic drugs, and the relationship between the prescription of anticholinergic medications and incidence of dementia or Alzheimer. If the necessary statistical data are unavailable in the primary studies, we will contact the corresponding authors, and within 10 days, three emails will be sent. We will inform all study authors that their research will be appropriately reported. If we do not receive an answer from the responsible author(s) of a given study after sending three emails, we will remove that study.

Approach to missing and incomplete data

If we face duplicate studies, we will employ one of these studies in the respective combination. We will use WebPlotDigitizer software if the data are graphical. However, if the data are not graphical, and obtaining missing data from published articles is indispensable, writers will attempt to contact the responsible author via email. If no response is received within 10 days and their data are related to the primary purposes of the present research, we will exclude the study.

Strategy for data synthesis

The relationship between the anticholinergic medications and dementia or Alzheimer risk will be analyzed by pooling odds ratio (ORs) with 95% confidence interval (CIs) in three models: predominant (TM+MM vs TT), recursive (MM vs TM+TT), and homozygote (MM vs TT) models using STATA Metan module. The Z test will evaluate significant odds ratio (ORs) values. Heterogeneity between selected articles will be evaluated with a statistical I^2 test; Higher I^2 values indicate higher levels of heterogeneity across the selected articles (Nyaga et al., 2014). For the Q test, the significance level will be considered <0.05 (Higgins et al., 2003).

Statistical analysis

In the present study, we will use Hazard and risk ratios as an approximation for the rate and ORs with a 95% confidence for dementia associated with cumulative exposure to anticholinergic drugs, adjusted for confounding variables. A random or fixed effect model will be used appropriately based on the selected studies' methodological similarities. If heterogeneity is confirmed across the studies, the usual random effects model (DerSimonian & Laird method) integrates the OR index (Jackson et al., 2010). This model simultaneously considers changes between studies and within studies. If meta-analysis is not feasible because of increasing methodological heterogeneity, then based on the results of the studies, only a qualitative narrative discussion will be presented. The Z test will be used to evaluate the significance of the degree of integrated OR, and a P<0.05 will be used as the significance basis of the hypothesis. Further, Forest plots will be drawn for all studies to display the separate and pooled effect size and their corresponding 95% CIs. Stata software, version 14.1 (Stata Corp, College Station, TX, USA) will be used in the present study.

Evaluation of heterogeneity

Statistical heterogeneity among primary studies will be assessed by the I^2 statistical test, Q-statistic test, and corresponding 95% CI (Higgins et al., 2011). We will interpret the I^2 coefficient using the following scoring: (0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% may represent considerable heterogeneity) (Deeks et al., 2008). For the Q test, the significance level will be considered to be less than 0.05 (Higgins et al., 2003).

Subgroup analysis

We will accordingly use subgroup analysis or meta-regression with a restricted maximum likelihood estimation method to investigate the impact of relevant factors on the development of statistical heterogeneity. All studies selected will be divided into different subgroups. In this study, prior subgroup analysis will be done for variables such as age group, gender, ethnicity, alcohol consumption, smoking, dementia or Alzheimer risk, quality of the study, the drug category, and different doses of the classified use.

Analysis of sensitivity

The researchers for sensitivity analysis will implement the one-out remove method. We will attentively check the characteristics of that study if one of the compositions (K-1) of the articles shows a different result than others.

Quality analysis

For quality analysis, we will assess the relationship between the methodological quality indexes of the primary articles. A reliable, valid, and trustworthy value of the composition of the articles with a minimum acceptable quality will be evaluated if there is remarkable diversity between the findings of the high-quality methodological studies and those of the poor-quality methodological studies.

Assessment of publication bias

If more than 10 studies are included in the review, the Funnel plot and Begg's and Egger's test will be used to assess the publication biases. If the previously mentioned methods show some evidence of publication bias, the trim and fill method will be used to correct the effect of publication bias. If the number of studies is fewer than 10, the publication bias cannot be calculated because of unreliability.

4. Discussion

Based on the publication bias assessment, the information obtained from this article will be completely reliable. However, our article may have some limitations. A high level of heterogeneity regarding the relation of those studies to the times and places, lack of strong population-based studies in most countries, and possible methodological bias in the preliminary studies are expected. It should be remembered that anticholinergic drugs have many different uses, and the rate of prescription of these drugs in recent years in people, especially older people, is increasing. Also, the results of different studies in this field are various. The findings of this study, along with other studies, will help physicians and other health professionals before prescribing these drugs; older people, especially those with polypharmacy, should be carefully assessed for the risk of dementia, Alzheimer or various cognitive disorders. To determine whether the effects of cognitive decline in these drugs are short-term or long-term will be determined in the future by conducting various primary and secondary studies.

Ethical Considerations

Compliance with ethical guidelines

The results of the present study will be published in peer reviewed journals and related conferences while observing ethical points. Ethical approval was granted by the Student Research Committee and Vice Chancellor of Research of Ahvaz Jundishapur University of Medical Sciences Ethics Committee, Ahvaz, Iran (Code: IR.AJUMS.REC.1399.173).

Funding

This research was supported by the research project (No.: 99s13), Funded by the University of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Authors' contributions

Supervision: Elham Maraghi; Methodology: Hadis Ashrafizadeh, Amal saki Malehi, Elham Maraghi, and Ali Reza Safarpour; Data collection: Hadis Ashrafizadeh, Maryam Hajmohammadi and Aliakbar Oroojan; Data analysis: Elham Maraghi; Amal Saki Malehi and Ali Reza Safarpour; Investigation: Hadis Ashrafizadeh and Aliakbar Oroojan; Funding administration: Hadis Ashrafizadeh; Writing the original draft: Hadis Ashrafizadeh, Maryam Hajmohammadi and Aliakbar Oroojan; Review & editing: All Author.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors acknowledge the Student Research Committee and Vice Chancellor of Research of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran for providing the necessary credentials for the present study.

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