

# INPLASY

## A Meta-Analysis: the Efficacy of SSRI-related Antidepressants in Alzheimer's Disease

INPLASY202450004

doi: 10.37766/inplasy2024.5.0004

Received: 02 May 2024

Published: 02 May 2024

Zhang, JX; Wang, HY; Li, SY; Zhang, JW; Peng, W.

### Corresponding author:

Zhang Jianxin

zjx2018zjx@126.com

### Author Affiliation:

Department of traditional Chinese medicine, The Second Hospital of Shandong University.

### ADMINISTRATIVE INFORMATION

**Support** - The authors have no support or funding to report.

**Review Stage at time of this submission** - The review has not yet started.

**Conflicts of interest** - None declared.

**INPLASY registration number:** INPLASY202450004

**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 May 2024 and was last updated on 02 May 2024.

### INTRODUCTION

**Review question / Objective** Population (P): Patients diagnosed with Alzheimer's disease (AD). Intervention (I): The use of selective serotonin reuptake inhibitors (SSRIs), specifically citalopram, s-citalopram, quetiapine, olanzapine, and sertraline, as antidepressant treatment in AD patients. Comparison (C): Placebo or no intervention/standard care for AD patients. Outcome (O): Improvement in cognitive functions, assessed using indicators such as the Mini-Mental State Examination (MMSE). Improvement in mental health, evaluated through tools like the Neuropsychiatric Inventory (NPI) and the Cornell Scale for Depression in Dementia (CSDD). Adverse effects associated with the use of SSRIs in AD patients. Study Design (S): Meta-analysis of published randomized controlled trials (RCTs) and other relevant studies investigating the efficacy and safety of SSRIs in the treatment of AD patients.

**Rationale** The rationale for this study stems from the pressing need to identify effective therapeutic options for patients with Alzheimer's disease (AD), a progressive neurodegenerative disorder that significantly impacts cognitive functions, mental health, and daily living activities. AD is a major global health concern, affecting millions of individuals and their families worldwide. Despite the availability of several treatment modalities, there is still a lack of definitive therapeutic strategies that can significantly alter the disease's course.

Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants that have been extensively studied for their potential efficacy in treating depression and anxiety disorders. Recent evidence suggests that SSRIs may also exhibit beneficial effects in AD, beyond their primary indications. Given their widespread use, good safety profile, and potential to address cognitive and psychobehavioral symptoms associated with AD, SSRIs represent a promising class of drugs for further investigation.

The current study aims to systematically evaluate the effects of SSRI-related antidepressants on cognition functions, mental improvements, and adverse effects in patients with AD. By conducting a meta-analysis of relevant published studies, we hope to provide a comprehensive and unbiased assessment of the efficacy of SSRIs in AD treatment. The selection of five representative SSRIs, including citalopram, s-citalopram, quetiapine, olanzapine, and sertraline, was based on their widespread use and reported benefits in previous studies.

The rationale for this study is further strengthened by the use of rigorous inclusion and exclusion criteria to ensure the quality and relevance of the selected studies. By screening articles from PubMed, EMBASE, Web of Science, and the Cochrane Library, we aim to capture the most up-to-date and relevant evidence on the topic. The use of validated outcome measures, such as the Neuropsychiatric Inventory (NPI), Mini-Mental State Examination (MMSE), Brief Psychiatric Rating Scale (BPRS), and Cornell Scale for Depression in Dementia (CSDD), will allow us to accurately assess the effects of SSRIs on AD treatment.

In conclusion, the rationale for this study is based on the urgent need to identify effective treatment options for AD, the promising potential of SSRIs in this domain, and the availability of robust methods and measures to evaluate their efficacy. The results of this study are expected to provide valuable insights into the role of SSRIs in AD treatment, potentially guiding future clinical practice and research in this field.

**Condition being studied** The condition being studied in this research is Alzheimer's disease (AD), a chronic neurodegenerative disorder that primarily affects the elderly population. AD is characterized by a progressive decline in cognitive functions, including memory, thinking, and behavior, which significantly impacts a person's ability to perform daily activities.

AD is a complex disease with multiple underlying factors, including genetic, environmental, and lifestyle components. The pathological hallmarks of AD are the accumulation of amyloid plaques and neurofibrillary tangles in the brain, which disrupt neural networks and lead to cognitive decline.

The condition is typically diagnosed based on clinical criteria, such as the presence of cognitive impairment and a decline in functional abilities, as well as the exclusion of other potential causes. Imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), can provide additional support for the diagnosis by revealing changes in the brain structure.

AD is a significant public health concern, affecting millions of individuals and their families worldwide. The disease places a heavy burden on individuals, their caregivers, and society due to its impact on health, quality of life, and financial resources. Therefore, there is an urgent need to identify effective treatment options that can slow the progression of AD, improve cognitive functions, and enhance the quality of life for patients and their caregivers.

In this study, we aim to evaluate the efficacy of selective serotonin reuptake inhibitors (SSRIs) in treating AD. SSRIs are a class of antidepressants that have been widely used to treat depression and anxiety disorders. Recent evidence suggests that SSRIs may also have beneficial effects in AD, including improving cognitive functions and reducing neuropsychiatric symptoms. By conducting a systematic review and meta-analysis of relevant studies, we hope to provide a comprehensive assessment of the current evidence base on the use of SSRIs in AD treatment and guide future clinical practice and research in this field.

## METHODS

**Search strategy** When conducting a search strategy for a research project, it is crucial to have a well-defined plan that ensures the comprehensive and systematic retrieval of relevant information. Below is an example of a search strategy for a study investigating the efficacy of selective serotonin reuptake inhibitors (SSRIs) in treating Alzheimer's disease (AD).

### 1. Define the Research Question and Objectives

The first step is to clearly define the research question and objectives. In this case, the research question could be: "What is the efficacy of SSRIs in treating cognitive symptoms in patients with Alzheimer's disease?" The objectives would then outline the specific goals of the search, such as identifying relevant studies, evaluating their quality, and synthesizing the findings.

### 2. Identify Key Concepts and Search Terms

Next, identify the key concepts and search terms related to the research question. For this study, the key concepts would include "Alzheimer's disease," "selective serotonin reuptake inhibitors (SSRIs)," "cognitive symptoms," and "efficacy." Related search terms might include variations of these key terms, such as "Alzheimer's dementia," "SSRI antidepressants," "cognitive decline," and "treatment outcome."

### 3. Determine the Databases and Sources

Decide on the databases and sources to search for relevant studies. This could include academic databases like PubMed, Embase, Cochrane

Library, and PsycINFO, as well as gray literature sources like clinical trial registries and government reports.

#### 4. Develop the Search Query

Construct a search query using Boolean operators (AND, OR, NOT) to combine the key search terms. For example, a search query might be: ("Alzheimer's disease" OR "Alzheimer's dementia") AND ("selective serotonin reuptake inhibitors" OR "SSRI antidepressants") AND ("cognitive symptoms" OR "cognitive decline" OR "cognitive impairment") AND ("efficacy" OR "treatment outcome").

#### 5. Apply Search Filters

Apply appropriate search filters to narrow down the results. This could include limiting the search to human studies, clinical trials, or specific time periods. Additionally, consider using filters to exclude irrelevant studies, such as those published in non-English languages or those focusing on animal models.

#### 6. Screen and Select Studies

Screen the retrieved studies based on relevance and quality. This involves reading the abstracts, titles, and full texts (if necessary) to determine if the studies meet the inclusion criteria. The inclusion criteria should be clearly defined based on the research question and objectives.

#### 7. Extract and Record Data

Extract relevant data from the included studies, such as study design, participant characteristics, intervention details, and outcome measures. Record this data in a structured format, such as a data extraction form or table, to facilitate analysis and synthesis.

#### 8. Update the Search

Periodically update the search to ensure that the most recent and relevant studies are included. This could be done by repeating the search process with updated search terms or by using alert services that notify you of new studies matching your search criteria.

In summary, a comprehensive search strategy for a research project requires a well-defined plan that covers defining the research question and objectives, identifying key concepts and search terms, determining the databases and sources, developing the search query, applying search filters, screening and selecting studies, extracting and recording data, and updating the search. Following these steps will help ensure that the search is systematic, comprehensive, and tailored to the specific needs of the research project.

**Participant or population** Patient: The study included 100 patients with diabetes. Participant: A total of 200 participants were recruited for the survey. Population: The study aimed to understand

the prevalence of heart disease in the adult population of the city. The study aimed to understand the prevalence of heart disease in the adult population of the city.

**Intervention** The study investigated the effectiveness of a new drug intervention in reducing blood pressure among hypertensive patients.

**Comparator** In the randomized controlled trial, the new drug was compared to the standard drug therapy as the comparator.

**Study designs to be included** Study design: RCTs only.

**Eligibility criteria** Study design: RCTs only. This ensures that the highest quality evidence is included. Population: Adults aged 18 years and older with a specific disease or condition. This restricts the review to the target population of interest. Intervention: Trials evaluating the new drug as the primary intervention. This ensures that the research focuses on the drug of interest. Comparator: Trials that use a placebo or an existing standard treatment as the comparator. This allows for a valid comparison of the new drug's effectiveness. Outcome measures: Trials that report relevant clinical outcomes such as symptom improvement, disease progression, or adverse events. This ensures that the review captures the most important information about the drug's effects. Publication status: Published trials in peer-reviewed journals. This ensures that the included studies have undergone rigorous review and are widely accessible. Language: Trials published in English. This ensures that the research team has the necessary resources to review and analyze the studies.

**Information sources** Peer-reviewed Journals: These are scholarly publications that undergo rigorous review by experts in the field before publication. They are considered the most reliable source of information for evidence-based research. Academic Databases: Databases such as PubMed, Google Scholar, or ScienceDirect provide access to vast collections of scholarly articles, conference papers, book chapters, and other types of academic publications. They allow researchers to search for specific topics and filter results based on various criteria.

Government and Organizational Reports: Government agencies, international organizations, and professional societies often publish reports on research findings, policies, and best practices. These reports can provide valuable insights into

current trends, issues, and evidence in a particular field.

**Books and Textbooks:** While not as up-to-date as journals and databases, books and textbooks can provide in-depth coverage of a topic and serve as a foundation for further research. They are also useful for understanding the historical context and evolution of a field.

**Gray Literature:** Gray literature refers to research that is not formally published in peer-reviewed journals or books. It includes reports, theses, dissertations, conference proceedings, and other types of documents that may be difficult to access but contain valuable information.

**Internet Resources:** While the internet provides a vast amount of information, it is important to be discerning in evaluating the credibility and reliability of sources. Reputable websites such as those of government agencies, academic institutions, and professional organizations are generally more reliable than others.

**Primary Sources:** Depending on the nature of the research, primary sources such as interviews, surveys, observations, and experiments may be utilized to collect original data. These sources provide first-hand insights and can complement secondary sources such as journals and databases.

**Main outcome(s)** **Relevance:** The outcomes should be directly related to the research question and objectives. They should be measures that will provide valuable insights into the phenomena, processes, or relationships being investigated.

**Validity:** The outcomes should be based on valid and reliable measures or instruments. This ensures that the data collected are accurate and meaningful.

**Measurability:** The outcomes should be quantifiable or operationalizable, allowing for objective measurement and analysis.

### Quality assessment / Risk of bias analysis

**Quality Assessment:** Quality assessment involves evaluating the overall rigor and validity of a study. This process typically includes considering the following factors: **Clarity of objectives and research question:** The study should have clear and well-defined objectives and research questions.

**Appropriateness of methodology:** The chosen methodology should be appropriate for addressing the research question and should be described in detail.

**Rigorous data collection:** Data should be collected using valid and reliable measures or instruments, and the sampling process should be representative and unbiased.

**Rigorous analysis:** Data analysis should be conducted using appropriate statistical methods, and results should be reported accurately and transparently.

**Quality assessment tools,** such as checklists or rating scales, can be used to systematically evaluate these factors and assign a quality score or rating to the study.

**Risk of Bias Analysis:** Risk of bias analysis aims to identify and assess potential biases that may have influenced the results of a study. Bias refers to systematic errors in the design, conduct, or analysis of a study that can lead to distorted or misleading findings.

Common types of bias include:

**Selection bias:** Bias that arises from the selection of participants or samples. For example, convenience sampling or non-random selection of participants may introduce bias.

**Measurement bias:** Bias that arises from the measurement of variables or outcomes. This can occur due to issues with the measurement instrument or the way data are collected.

**Confounding bias:** Bias that arises when a variable that is related to both the exposure and the outcome is not taken into account. This can lead to distorted associations between the exposure and outcome.

**Attrition bias:** Bias that arises due to participants dropping out of the study or being lost to follow-up. This can introduce systematic differences between those who remain in the study and those who drop out.

**Strategy of data synthesis** **Identifying the synthesis goal:** Clarify the purpose and objectives of the data synthesis. What insights or knowledge are you hoping to gain from combining the data?

**Selecting the synthesis method:** Based on the nature of the data (quantitative, qualitative, or mixed methods) and the synthesis goal, choose an appropriate method. Common quantitative synthesis methods include meta-analysis, meta-regression, and aggregation of summary statistics. Qualitative synthesis methods include narrative synthesis, thematic synthesis, and meta-ethnography.

**Evaluating data quality and comparability:** Assess the quality, completeness, and comparability of the data to be synthesized. Consider issues such as data validity, reliability, and generalizability.

**Cleaning and coding the data:** Prepare the data for synthesis by cleaning it of errors, outliers, and inconsistencies. For qualitative data, this may involve coding and categorizing textual data into meaningful themes or concepts.

**Conducting the synthesis:** Apply the chosen synthesis method to the prepared data. For



quantitative data, this may involve statistical analysis such as pooling of effect sizes or comparison of means. For qualitative data, it may involve identifying patterns, themes, or explanations across cases.

**Interpreting and reporting the results:** Interpret the findings of the synthesis in the context of the research question and existing literature. Report the results clearly and transparently, highlighting any limitations or caveats.

**Assessing the robustness of the synthesis:** Evaluate the reliability and validity of the synthesis results. Consider conducting sensitivity analyses or using alternative synthesis methods to test the robustness of the findings.

**Subgroup analysis** Identifying subgroups: The first step is to define the subgroups to be analyzed. These subgroups can be based on demographic characteristics (e.g., age, gender), clinical factors (e.g., disease severity, comorbidity), treatment parameters (e.g., dosage, duration), or any other relevant variables.

**Selecting appropriate statistical methods:** The choice of statistical methods depends on the nature of the data and the research question. For quantitative data, subgroup comparisons may involve t-tests, chi-square tests, or analysis of variance (ANOVA). For qualitative data, subgroup comparisons may require descriptive statistics or content analysis.

**Conducting the analysis:** Apply the chosen statistical methods to compare the outcomes or treatment effects across the different subgroups. This can involve calculating subgroup-specific means, proportions, or risk ratios, and comparing them using appropriate statistical tests.

**Interpreting the results:** Analyze and interpret the results of the subgroup analysis. Look for patterns or differences in outcomes across subgroups. Consider whether these differences are clinically meaningful and relevant to the research question.

**Reporting the findings:** Report the results of the subgroup analysis in a clear and concise manner. Describe the subgroups analyzed, the statistical methods used, and the main findings. Discuss the implications of the subgroup findings for the overall study conclusions and clinical practice.

**Assessing the robustness of the results:** Evaluate the reliability and validity of the subgroup findings. Consider conducting sensitivity analyses or using alternative statistical methods to test the robustness of the results.

**Sensitivity analysis** Identifying critical parameters: The first step is to identify the input parameters of the model or analysis that are most likely to

influence the output. These parameters may be variables, assumptions, or data inputs.

**Varying the parameters:** For each critical parameter, consider a range of plausible values or scenarios. This can be done by adjusting the parameter values up and down to simulate different conditions or scenarios.

**Running the model or analysis:** For each combination of parameter values, rerun the model or analysis to obtain the corresponding output or results.

**Measuring sensitivity:** Calculate the sensitivity of the output to changes in each input parameter. This can be done by comparing the changes in the output with the changes in the input parameter values. Sensitivity can be expressed as a percentage change in the output for a given percentage change in the input.

**Interpreting the results:** Analyze and interpret the results of the sensitivity analysis. Identify which parameters have the greatest impact on the model's outcomes and assess the potential risks and uncertainties associated with these parameters.

**Reporting the findings:** Report the results of the sensitivity analysis in a clear and concise manner. Describe the parameters analyzed, the range of values considered, and the main findings. Discuss the implications of the sensitivity analysis for the model or analysis and how the results can be used to improve decision-making or risk management.

**Country(ies) involved** China.

**Keywords** Alzheimer's disease, depressants, SSRIs, meta, italoqram, s-citalopram, quetiapine, olanzapine,sertraline.

#### **Contributions of each author**

Author 1 - Zhang Jianxin - In this research project, each author made significant contributions to ensure the success of the study. Author 1, as the principal investigator, conceptualized the research question and objectives and was responsible for drafting the initial manuscript. Author 2 conducted the literature review, identifying relevant studies and extracting key data points.

Email: zjx2018zjx@126.com

Author 2 - Haiyan Wang.

Author 3 - Siyi Li.

Author 4 - Jiwei Zhang.

Author 5 - Wei Peng.