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Quality of evidence supporting the role of non-steroidal anti-inflammatory drugs for the treatment of anxious depression: a protocol for an overview of systematic reviews and meta-analyses

Chengda Dong ![ORCID],[1] Hongshuo Shi,[2] Zhaojun Yan,[3] Guomin Si,[4] Jianmin Liu[3]

For numbered affiliations see end of article.

Correspondence to
Dr Jianmin Liu;
2021100085@sdutcm.edu.cn

ABSTRACT

Introduction There have been several studies showing the effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) for anxious depression. We aimed to summarise the evidence and evaluate the methodological quality regarding the effectiveness and safety of NSAIDs for anxious depression from systematic reviews/meta-analyses (SRs/MAs).

Methods and analysis Two researchers searched seven databases for SRs/MAs, which are randomised controlled trials on NSAIDs for anxious depression. Two investigators used the Assessment System for Evaluating Methodological Quality 2, the Risk of Bias in Systematic reviews tool, the list of preferred reporting items for SRs/MAs and the Grading of Recommendations, Assessment, Development and Evaluation system to assess the included SRs/MAs.

Ethics and dissemination The findings of the study will be disseminated through peer-reviewed journals, and national and international conference presentations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study provides the first overview of systematic reviews/meta-analyses (SRs/MAs) that focuses on the safety and effectiveness of non-steroidal anti-inflammatory drugs for anxious depression.
⇒ The Assessment System for Evaluating Methodological Quality 2 tool is used in assessing the methodological quality of the included SRs/MAs.
⇒ The Risk of Bias in Systematic reviews tool is used in assessing the risk of bias in the included SRs/MAs.
⇒ This study involves SRs/MAs based on randomised controlled trials.
⇒ This study excludes network meta-analyses, so a small subset of studies may missing.

INTRODUCTION

Major depressive disorder (MDD) is one of the most common clinical psychiatric disorders. It is a type of mood disorder characterised by significant and persistent depression from various causes, with a lifetime prevalence of about 16%.[1] In addition to common physical comorbidities, patients with depression often have a co-occurring anxiety disorder (AD). According to the Diagnostic and Statistical Manual of Mental Disorders, fifth Edition criteria, it uses 'with anxiety distress descriptor' in its MDD section to define anxious depression. Epidemiological studies and clinical research have found that approximately 60%–90% of patients with MDD have co-occurring anxiety symptoms or co-occurring ADs,[2 3] which typically result in more severe functional impairment, greater antidepressant resistance, higher risk of suicide and disability, and lower quality of life for patients with MDD,[4] complicating the treatment process and worsening clinical outcomes. Although MDD and AD are highly heterogeneous diagnostic categories, they show significant comorbidities that may share some aetiological mechanisms.[5 6] An important barrier to the effective treatment of anxious depression is the incomplete understanding of the underlying biological mechanisms and how drugs and other interventions work at the cellular molecular level.

In the current treatment strategy for anxiety depression, oral medications, such as SSRI, SNRI, bupropion, etc, are preferred. However, antidepressants may aggravate patients' anxiety symptoms in the initial stage of treatment, so they are often used clinically in smaller doses to start and slowly increase, or combined with benzodiazepines such as clonazepam and alprazolam to exert anxiolytic effects, but long-term use is not recommended.[7] This has resulted in problems such as the prolonged onset of medication, a complication of medication and long duration of medication, as well as multiple

possible adverse effects caused by antidepressants and anxiolytics, all of which pose challenges to the treatment of anxious depression.

Recently, research on the involvement of inflammation in the onset and development of anxious depression by affecting neurobiochemistry, etc has become a hot topic in this area. Neurodegenerative and neurotoxic effects of inflammatory markers and activation of proinflammatory cytokines on the central nervous system and glial cells have been shown to be involved in the development of depression and ADs.[8–10] Based on the hypothesis of the inflammatory mechanism of depression, some researchers have proposed non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of depression. NSAIDs reduce levels of inflammatory factors in an anti-inflammatory manner to achieve antidepressant effects, and many studies confirmed the effectiveness of NSAID treatment in improving depressive and anxious symptoms, cognitive function and somatic discomfort in patients. There have been several studies showing the effectiveness of NSAIDs for anxious depression.

Systematic reviews (SRs)/meta-analyses (MAs) are thought to be the reliable criteria for the evaluation of the effectiveness of certain therapeutic interventions, but their methods must strictly adhere to a series of guidelines to minimise the bias in answering specific research questions.[11] However, a large proportion of SRs/MAs researchers do not strictly adhere to the above criteria. This reduces the quality of reviews and poses an obstacle to providing convincing results and conclusions. A systematic overview of SRs/MAs is a relatively new approach for synthesising the outcomes from multiple SRs/MAs, evaluating their quality and attempting to address any inconsistent outcomes. We obtained several published MAs/SRs that reported the effectiveness of anti-inflammatory treatment on anxious depression by searching several necessary databases, but their quality of evidence and methodology have not been evaluated. Therefore, we designed and composed an overview to summarise the evidence on the safety and effectiveness of NSAIDs for anxious depression.

METHOD
Research registration

This overview of MAs/SRs is strictly based on the following criteria: Preferred Reporting Items for Overviews of Systematic Reviews including the harms checklist.[12] Our study is a secondary study based on clinical research. Therefore, no ethical approval is required.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (A) study design: SRs/MAs based on randomised controlled trials (RCTs); (B) participants: the participants had anxious depression diagnosed according to any authoritative diagnostic criteria, no restrictions on sex, race, age, onset time or the source of cases; (C) intervention: NSAIDs (including oral

Table 1 Search strategy of PubMed

#1	"Depressive disorder"(Mesh) OR "Depressive Symptom"(Title/Abstract)OR "Emotional Depression"(Title/Abstract)OR "Major depressive disorder"(Title/Abstract)
#2	"Anxiety Disorders"(Mesh) OR "Anxiety Symptom"(Title/Abstract)OR "Anxious"(Title/Abstract)
#3	#1 AND #2
#4	"Anti-Inflammatory Agents"(Mesh) OR "Nonsteroidal Anti-inflammatory Drug"(Title/Abstract)OR "NSAID*"(Title/Abstract)OR "Anti-Inflammatory treatment"(Title/Abstract) OR "Anti-Inflammatory treatment therapy"(Title/Abstract)OR "Anti-Inflammatory"(Title/Abstract)
#5	"systematic review"(Title/Abstract)OR "meta-analysis"(Title/Abstract)OR "meta-analysis"(Title/Abstract)OR "systematic review"(PT) OR "Systematic Reviews as Topic"(Mesh) OR "meta-analysis"(pt) OR "Meta-Analysis as Topic"(Mesh)
#6	#3 AND #4 AND #5

and injectable NSAIDs) versus conventional antidepressants or NSAIDs combined with conventional antidepressants versus conventional antidepressants alone and (D) outcomes: effective rate (efficiency of NSAIDs for anxious depression reported in each included article), Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Treatment Emergent Symptom Scale, potential gastrointestinal and neurological adverse events, etc.

The exclusion criteria were as follows: (A) animal studies; (B) overviews, network MAs and narrative reviews; (C) studies in which the required data were unavailable and (D) conference abstract.

Search strategy

Two independent researchers conducted a literature search. Literature searches were conducted in the Cochrane Library, PubMed, Web of Science, EMBASE, China National Knowledge Infrastructure (CNKI), SinoMed, Chongqing VIP and from their inceptions to 1 August 2022. Search queries are composed of a combination of MeSH Terms, keywords and free words. We also manually searched the references of related articles. The specific search strategy is modified according to different databases. Table 1 demonstrates the search strategy for the PubMed database.

Eligibility assessment and data extraction

Two researchers independently screened the retrieved documents. The specific steps were as follows: first removed duplicate publications, then read the title abstract to exclude the studies that do not meet the criteria, and finally read the full text to determine its eligibility (figure 1). Any disagreements in the evaluation process will be resolved by the third reviewer through arbitration and negotiation. The following data were extracted by two independent researchers: first author, year of publication, country, number of included trials and participants, interventions, results, quality assessment methods and the main conclusions of each included review.
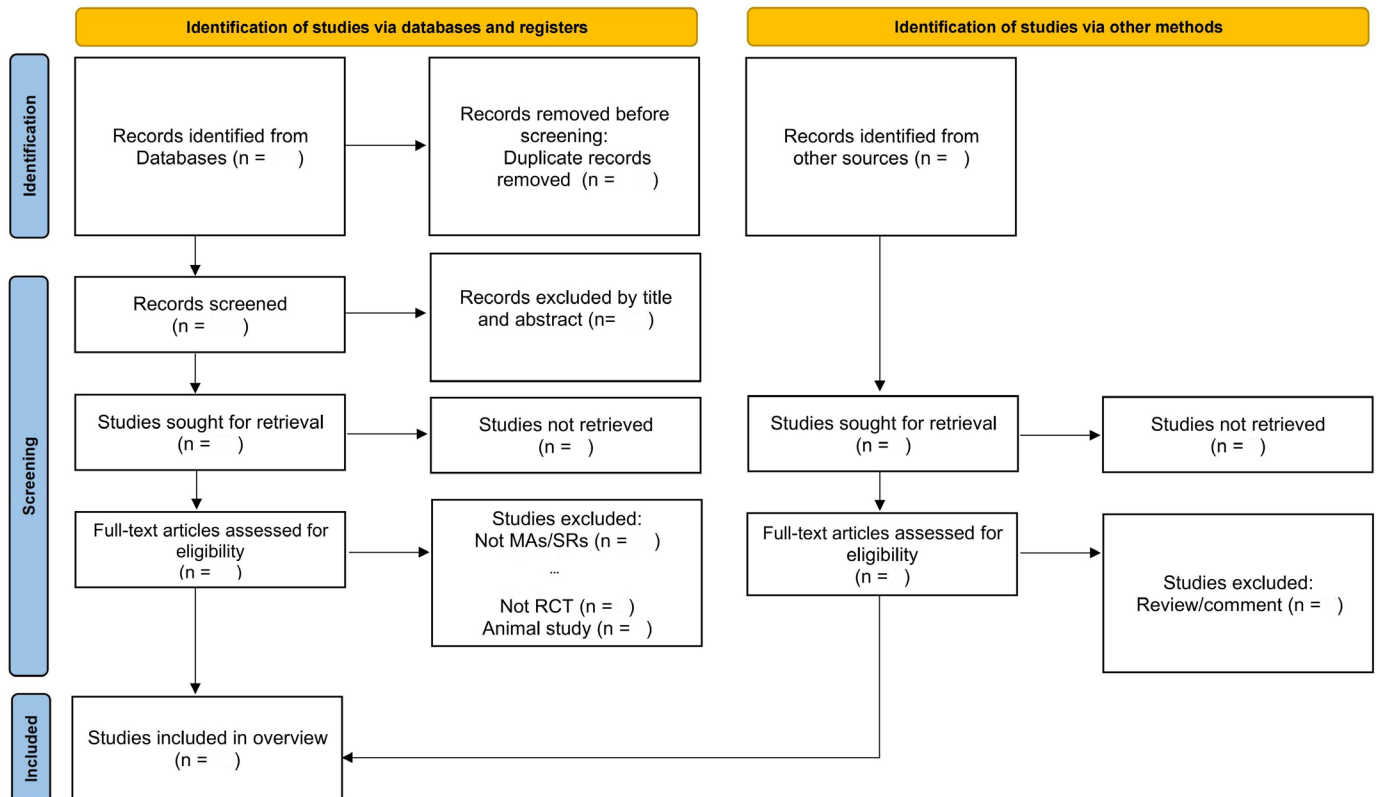
Figure 1 The details of the literature selection process. MAs, meta-analyses; RCTs, randomised controlled trials; SRs, systematic reviews.

SRs/MAs quality assessment

Assessment of methodological quality

The Assessment System for Evaluating Methodological Quality 2[13] scale was used in assessing the methodological quality of the included SRs/MAs. It consists of 16 items, 7 of which are critical areas (2,4, 7, 9, 11, 13 and 15). Each item contains three evaluation options: yes, partially yes or no. After the reviewers' evaluation, the quality of each item was categorised into four levels, namely, critically low, low, moderate and high. The definition of the four quality classification is shown in table 2. Two reviewers independently evaluated the methodological quality of the included studies, and any disagreement arising during the assessment was settled by discussion or consultation with a third reviewer.

Assessment of risk of bias

The Risk of Bias in Systematic reviews (ROBIS) tool[14] was used in assessing the risk of bias in the included SRs/MAs, mainly focusing on four major categories of reviews: interventions, diagnosis, prognosis and aetiology. The results are judged as 'low', 'unclear' or 'high'. Two reviewers independently evaluated the risk of potential bias in included studies, and any disagreement arising during the assessment was settled by discussion or consultation with a third reviewer.

Assessment of reporting quality

The list of The Preferred Reporting Items for SRs and MAs[15] was adopted to assess the quality of each included

Table 2 Quality classification of the AMSTAR2

Quality classification	Definition
High	None or only one non-critical item does not meet the requirement: SRs/MAs provide accurate and comprehensive summaries of research questions based on the results of available research.
Moderate	More than one non-critical item does not meet the requirement*: Based on the results of available studies, SRs/MAs may provide accurate summaries.
Low	One critical item does not meet the requirement with or without non-critical item does not meet the requirement: SRs/MAs may not provide an accurate and comprehensive summary based on the results of available studies.
Critically low	More than one critical item does not meet the requirement, with or without non-critical item does not meet the requirement: Based on the results of available studies, it is not possible for SRs/MAs to provide an accurate and comprehensive summary.

*When multiple non-critical items do not meet the requirements, it will reduce the confidence in the system evaluation, which can be degraded from moderate to low quality.
AMSTAR2, Assessment System for Evaluating Methodological Quality 2; MAs, meta-analyses; SRs, systematic reviews.

SR/MA report based on the following areas: (A) title, (B) summary, (C) introduction, (D) method, (E) result, (F) discussion and (G) funding. The assessment form consists of 27 items and focuses on reporting methods and results in the meta-analysis. By determining the completeness of the information reported for each item, each item was designated as 'yes' (complete reporting), 'partially yes' (partial reporting) or 'no' (no reporting).

Assessment of quality of evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system[16] was used to assess the quality of the evidence of the included SRs/MAs, downgrading from five aspects: research limitations, inconsistencies, indirectness, imprecision and publication bias. The evidence quality was independently evaluated by two reviewers, and did the GRADE by themselves on the RCTs included in the reviews, and any disagreement arising during the assessment was settled by discussion or consultation with a third reviewer.

Data synthesis and presentation

An objective description was used in this overview. The characteristics and results of each SR/MA and the evaluation results of Assessing the Methodological Quality of Systematic Reviews 2, ROBIS, Preferred Reporting Items for Systematic Reviews and Meta-Analyses and GRADE are reported in the form of a list.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

DISCUSSION

Recent studies have shown that neuroimmune inflammation affects neurotransmitter and neuroendocrine levels and is strongly associated with the development of depression and anxiety, and the hypothesis of NSAIDs for depression was born. Several studies have indeed shown that antidepressants combined with NSAIDs help to alleviate depressive and anxiety symptoms and somatic symptoms, reduce inflammatory indicators, and improve cognitive function and various neurodegenerative disorders in patients. The evidence of the effectiveness of these NSAIDs is expected to guide the use of these drugs in the treatment of anxious depression and its accompanying somatic symptoms in the future, helping patients to return to society. There have been several relevant clinical trials of SRs/MAs to explore the efficacy of NSAIDs for anxious depression, and on this basis, we conducted a comprehensive evaluation of SRs/MAs of different quality, further explored the reliability of the results, and provided a theoretical basis for clinical and scientific researchers to conduct related research in the future.

ETHICS AND DISSEMINATION

The findings of the study will be disseminated through peer-reviewed journals, and national and international conference presentations.

Author affiliations
[1]First School of Clinical Medicine, Shandong University of Traditional Chinese Medicine, Jinan, China
[2]College of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, China
[3]Department of psychosomatic Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China
[4]Department of Traditional Chinese Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China

ORCID iD
Chengda Dong http://orcid.org/0000-0001-7369-9201

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