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Exploring the Dose–Response Relationship Between Acupuncture and Adverse Events: An Example From Overview of Systematic Reviews on Acupuncture for Chronic Pain Conditions

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ADMINISTRATIVE INFORMATION

Support - None.

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

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 April 2025 and was last updated on 15 April 2025.

INTRODUCTION

Review question / Objective Do some factors contributing to acupuncture dose have potential relationship with adverse events of acupuncture in chronic pain conditions?
Population: Chronic pain conditions including chronic neck pain, low back pain, osteoarthritis, headache or shoulder pain (pain duration should be at least 4 weeks)
Intervention: Manual acupuncture
Comparator: No treatment or sham acupuncture
Outcome: Type of adverse events (AEs), frequency of AEs, severity of AEs
Study design: Systematic reviews.

Rationale Because acupuncture is a non-drug intervention that affects the human body through mechanisms different from those of medications, it is generally not possible to determine its dose based on pharmacodynamics or pharmacokinetics, which are commonly used for drug dosing. In this context, the only viable method for determining optimal dose of acupuncture for specific conditions may be through clinical studies that evaluate the relationship between acupuncture dosage and treatment response. From this perspective, randomized controlled trials (RCTs) have been conducted to assess the dose-response relationship (in terms of effectiveness or efficacy) of acupuncture. For example, one RCT investigating acupuncture for knee osteoarthritis (OA) compared the effectiveness of treatments administered three times per week versus once per week. Patients who received acupuncture three times a week showed significantly better outcomes compared to those who received it once a week. This study suggests that, in the context of dose-effectiveness, the optimal frequency of acupuncture for knee OA appears to be closer to three times per week than once. In another example, a systematic review (SR) on functional recovery after stroke examined the relationship between acupuncture dose and therapeutic outcomes. The included RCTs were grouped into low-dose and high-dose categories based on factors such as treatment frequency, needle retention time, and overall treatment

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duration. By comparing the effect sizes across these subgroups, the review aimed to identify a potential optimal dose. Such studies demonstrate that it is possible to determine an appropriate level of acupuncture dosing that maximizes therapeutic effect.

However, these dose-response studies have focused solely on effectiveness. Currently, there is a lack of data on how acupuncture dose relates to adverse events (AEs), or what would constitute a reasonable dose when AEs are taken into consideration. While acupuncture is generally regarded as a safe intervention when performed by trained practitioners in appropriate settings, its invasive nature inherently carries risks such as bleeding or traumatic injury. Minimizing these AEs is an important aspect of clinical practice. If a relationship exists between acupuncture dose and the frequency or severity of adverse events, it becomes necessary to consider these risks when determining the optimal dose. Therefore, the purpose of this review is to conduct an overview of SRs that evaluate AEs with acupuncture for various chronic pain conditions, and to indirectly explore the potential relationship between acupuncture dose and the occurrence of AEs.

Condition being studied We will include systematic reviews (SRs) on chronic pain conditions including chronic neck pain, low back pain, osteoarthritis, headache or shoulder pain. Duration of pain for these conditions should be at least 4 weeks.

METHODS

Search strategy Pubmed, Embase, Cochrane Library will be searched and any SRs published before March 2025 will be included. Search strategies will be constructed by combining thesaurus terms and text words tailored to each database. "chronic neck pain", "chronic low back pain", "chronic osteoarthritis", "chronic headache" or ""chronic shoulder pain" and "acupuncture" will be used for searching. Specialized filters for study design (SR) will be used according to each database. Search strategy for Pubmed is as follows:
("Neck Pain"[MeSH Terms] OR "neck pain"[Title/Abstract] OR "chronic neck pain"[Title/Abstract] OR "Low Back Pain"[MeSH Terms] OR "low back pain"[Title/Abstract] OR "chronic low back pain"[Title/Abstract] OR "Osteoarthritis"[MeSH Terms] OR "osteoarthritis"[Title/Abstract] OR "chronic osteoarthritis"[Title/Abstract] OR "Headache"[MeSH Terms] OR "headache"[Title/Abstract] OR "chronic headache"[Title/Abstract] OR "Shoulder Pain"[MeSH Terms] OR "shoulder pain"[Title/Abstract] OR "chronic shoulder pain"[Title/Abstract]) AND ("Acupuncture Therapy"[MeSH Terms] OR "acupuncture"[Title/Abstract]) AND ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "systematic review"[Title] OR "meta-analysis"[Title] OR systematic[sb]).

Participant or population Patients with chronic pain conditions including chronic neck pain, low back pain, osteoarthritis, headache or shoulder pain (pain duration should be at least 4 weeks).

Intervention Patients with chronic pain conditions including chronic neck pain, low back pain, osteoarthritis, headache or shoulder pain will be included in this review. Pain duration should be at least 4 weeks.

Comparator Control intervention needs to include no treatment or sham acupuncture.

Study designs to be included Only SR of randomized controlled trials (RCTs) will be included. If several SRs for the same conditions are located from database searching, only updated and the largest SR will be included in the analysis.

Eligibility criteria Any SRs which do not include detailed information of the RCTS (or reference list) in the review will be excluded in this review.

Information sources Electronic databases including Pubmed, Embase, Cochrane Library will be searched up to April, 2025. Reference lists of the included SRs will be assessed and any SRs in the reference will be evaluated. Trial registry will not be searched because SRs will be included in this review. Authors of the included SRs will be contacted if necessary.

Main outcome(s) In this review, the primary outcomes are types, severity, and frequency of AEs after the end of treatment. Serious adverse events (SAEs) are defined as events that meet any of the following criteria including result in death, life-threatening events requiring hospitalization or prolongation of existing hospitalization or resulting in persistent or significant disability. The frequency of SAE and non-SAE cases reported in each study will be analyzed.

Quality assessment / Risk of bias analysis In this study, we will not conduct our own risk of bias (ROB) assessment; instead, we will extract the assessments reported in the included SRs and use

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them to assess the ROB of individual RCTs included in the review.

Strategy of data synthesis This study aims to test the association between factors constituting the dose of acupuncture and the frequency of adverse events (both serious adverse events [SAEs] and non-SAEs) using a meta-regression approach. Specifically, we will assess the relationships between various dose-related variables—such as the number of acupoints used per session, total number of treatment sessions, treatment frequency per week, stimulation intensity (strong vs. weak), elicitation of deqi, intervals between sessions, acupuncture retention time, needle thickness and length, depth of insertion—and the types, severity, and frequency of AEs. Data on acupuncture interventions and AEs will be extracted from the RCTs included in at the selected SRs of chronic pain conditions. Meta-regression analyses will be conducted using functions such as metareg from the meta package in R software.

Subgroup analysis Adverse events will be classified into SAEs and non-SAEs according to their severity, and the difference in frequency will be analyzed through subgroup analysis.

Sensitivity analysis As this is an exploratory study, no specific sensitivity analyses will be conducted.

Country(ies) involved Korea.

Keywords acupuncture; dose; adverse event; systematic review; meta-regression.

Contributions of each author

Author 1 - Tae-Hun Kim - Author 1 will conduct SR and will draft the manuscript.
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