Review Article

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How to conduct an acupuncture dose–effect relationship study? A discussion based on study methodology

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Abstract

Acupuncture therapy is widely used in the clinic, and its therapeutic effects have been proven by numerous studies. The dose–effect relationship of acupuncture is a fundamental aspect of the acupuncture research system. Recent studies found that different acupuncture dosages altered study results directly, indicating the importance of screening the optimal stimulation dosage. However, the system for studying the acupuncture dose–effect relationship is still in its infancy, and the methodology of the system needs to be improved. This review aimed to define the factors impacting acupuncture "dosage" and "effect," and to improve the methodological system for research on the dose–effect relationship of acupuncture. By summarizing the current findings of acupuncture dose–effect studies, we discussed the vital acupuncture parameters and methodological problems that influence the relationship between acupuncture dosage and its effects. These factors consist of specific influencing factors (acupoint selection, acupuncture manipulation parameters, *de qi* response) and nonspecific influencing factors (comparison selection, blinding procedure, patient expectancy). Our perspectives offer suggestions for the design of acupuncture dosage–effect trials. Further studies need to be conducted to establish the methodological system and provide systematic evidence of the acupuncture dose–effect relationship.

Keywords: Acupuncture, Dose–effect relationship, Methodology, Review

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Introduction

Acupuncture therapy originated from traditional Chinese medicine and is widely used as the complementary and integrative therapies over the world[1]. Through needle manipulations, acupuncture is used to regulate the *qi* and blood, and balance *yin* and *yang* of the body[2]. The stimulation dosage is a fundamental element of acupuncture, and is a vital facet of acupuncture manipulation, which determines the therapeutic effects of acupuncture[3]. The acupuncture dose–effect relationship was formulated more than 2,000 years ago in China. In the 1970s, academician Shi Xuemin defined the concept of the acupuncture dose–effect relationship, which contains the acupuncture method and the stimulation dosage of acupuncture[4]. By conducting a series of clinical trials and experimental research, academician Shi Xuemin preliminarily revealed the dose–effect relationship between manipulation parameters and the therapeutic effects of acupuncture, and established a system for studying the acupuncture dose–effect relationship. Exploration of the acupuncture dose–effect relationship can help to define the optimal parameters for acupuncture, which can provide the basis for the standardization of acupuncture therapy. Additionally, it is of great significance for the international promotion of acupuncture use.

According to the Consolidated Standards of Reporting Trials statement, sufficient details to allow replication is required when describing an intervention[5]. Acupuncture therapy should thus be accompanied by quantified manipulation details. To guide the reporting of acupuncture studies, the STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) stressed the importance and necessity of reporting details of acupuncture intervention, which led to improvements in the quality of trials reporting on acupuncture. In 2010, the revised STRICTA was published, which focused on the nonpharmacologic treatment properties

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of acupuncture[6]. The description of needling details has been extended into 6 sub-items including the number of acupoints, acupoint selection, needle depth, *de qi* response, needle stimulation, needle retention time, and needle type. In terms of the treatment regimen, the number, frequency, and duration of treatment sessions are required to be reported.

In the same way, pharmaceutical treatment is established with the optimal appropriate dosage, treatment frequency, and treatment duration[7]. The concept of acupuncture "dose" is the true stimulation dosage of acupuncture, which means the aggregation of individual sessions over the treatment course[8]. Each acupuncture treatment session is mechanical stimulation, and the dosage is dependent on a compound of parameters involving needling depth, needling direction, needling depth, manipulation frequency, the frequency of acupuncture session, and the whole treatment duration. For clinical application, the dose has three important aspects: the minimal stimulating dosage that elicits sufficient therapeutic effect[9], the maximal stimulating dosage that avoids adverse reactions[10], and the optimal stimulating dosage for the specific disease[11]. As for the "effect" in the clinical study, it is related to the therapeutic effect such as the modulation of dysfunction and the recovery of deformity. The differential stimulation dosage on acupoints has a diverse influence on the downstream conduction pathways *via* the nerve system, endocrine system, and immune system, or has a differential impact on the target organs directly, which changes the therapeutic effects. While in the experimental research, the "effect" refers to the whole process of effective pathways from the initial evoking effect of acupoint[12], the amplification effect of the signal pathway conduction[13], the modulation effect of the neuro-endocrine-immune network[14], and the regulation effect of organs[15].

In an acupuncture dose–effect relationship study, multiple factors are associated with dose and effect. They are divided into specific influencing factors (acupoint selection, acupuncture manipulation parameters, *de qi* response) and nonspecific influencing factors (comparison selection, blinding procedure, patient expectancy) in this review. Acupuncture manipulation parameters and acupoint selection are fundamental elements of acupuncture dosage. From a methodological point of view, having quantified manipulation parameters benefits the repeatability of acupuncture research, improving the intervention consistency in multi-center studies, which helps to reduce the heterogeneity arising from acupuncture operations[6]. In terms of clinical effect, the direct impact of acupuncture manipulation parameters on changes in clinical effects have been proven, which emphasizes the significance of exploring the optimal acupuncture parameter[16–19]. For instance, a previous study demonstrated that changes in acupuncture twirling frequency evoked different mechanistic pathways[20]. A series of randomized clinical trials (RCTs) with differences in acupuncture treatment sessions presented contrasting results on the effects of acupuncture for treating knee osteoarthritis (KOA)[21-22]. Considering the diverse study results, adequate acupuncture dosage is of great significance. Therefore, the exploration of the acupuncture dose–effect relationship is a potent way to address contradictory conclusions. It also facilitates establishing the mechanistic pathways underlying acupuncture effects. However, studies of acupuncture dose–effect requires a distinct methodological system.

The objective of this review is to identify crucial factors that influence acupuncture dosage, acupuncture effects, and their relationship, and to propose practicable solutions from a study methodological point of view. We hope to provide up-to-date evidence for establishing a system for evaluating the acupuncture dose–effect relationship.

Vital methodological strategies in studies of the acupuncture dose–effect relationship

Specific factors influencing the dose–effect relationship

Acupoint selection

Acupoints are the basic components of the meridian system and are the minimal unit that contributes to the acupuncture effect. According to traditional Chinese medicine theory, each acupoint has particular therapeutic properties, and the combinations of different acupoints show different therapeutic effects. Currently, studies of the acupuncture dose–effect relationship typically uses a single acupoint or a particular acupoint regimen. Single acupoint studies usually choose a specific acupoint whose therapeutic effects have been proven based on a sufficient number of clinical cases. For instance, in the study of acupuncture at ST36 (Zusanli) for sepsis, experimental research has presented the mechanisms at molecule, cell, tissue, organ, and whole-body levels[23]. One distinct strength of single acupoint studies is that this can reduce bias caused by other acupoints, hence revealing the real effects of the selected acupoint. Moreover, the intervention procedure is less complicated than acupoint combination studies. However, single acupoints might not meet the clinical requirements: the combination of other acupoints with similar effects is typically necessary. In acupoint combination studies, researchers mostly focus on comprehensive effects, including the clinical therapeutic effects and the mechanistic pathways. The relationship between acupoint selection and the acupuncture dose–effect relationship is demonstrated in Figure 1. Generally speaking, both single acupoint studies and acupoint combination studies should consider different dosages as variables in acupuncture dose–effect relationship studies. These dosage variables could involve manipulation parameters, including needle depth, needle twirling frequency (or electroacupuncture frequency), needle direction, needle retention time, and treatment sessions. We analyzed these manipulation parameters in the following part.

Acupuncture manipulation parameters

The acupuncture manipulation parameter is the core factor that influences the stimulation dosage, and thus alters acupuncture effects directly. Based on current study evidence, we illustrate the relationship between manipulation parameters and effects such as needle depth, needle manipulation frequency (or electroacupuncture frequency), needle direction, needle retention time, and treatment sessions.

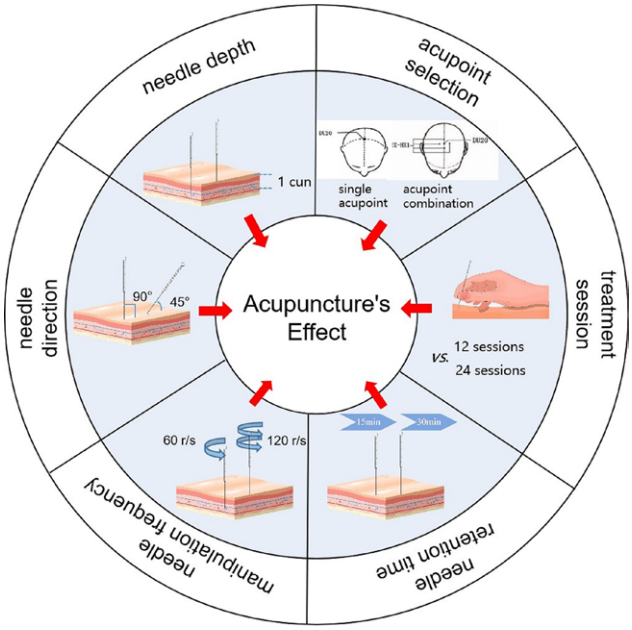

Figure 1. Relationship between acupuncture dosage and effect. Acupuncture dosage-related factors include acupoint selection, treatment session, needle manipulation frequency, needle retention time, needle direction, and needle depth.

Needle depth affects the acupuncture effects by stimulating specific anatomical tissues. For example, superficial acupuncture at RN23 (Lianquan) stimulates the cutaneous nerve of the neck, while in-depth acupuncture stimulates the thyrohyoid muscle, the tongue muscle, the superficial anterior jugular vein, the superior thyroid artery, the superior thyroid vein, and the hypoglossal nerve[24]. In a study of the effects of acupuncture at RN 23 on dysphagia, a deep acupuncture group (needle depth of 60–70 mm) showed greater effects in terms of improved clinical symptoms than did a shallow acupuncture group (needle depth of 10–20 mm)[25]. However, other studies obtained variable results, indicating that the optimal needle depth varies with the disease severity[26] and with the patients' condition[27].

Acupuncture direction is closely associated with the effects and safety of acupuncture therapy[10]. It has been described in detail in China since ancient times. The acupuncture direction is flexible and is changed for different diseases. According to traditional Chinese medicine theory and the meridian system, acupuncture direction can be determined by the meridian trajectory and the body projection area of the disease. In the modern medical system, studies of acupuncture direction have been extended, taking into account the anatomical characteristics of the nervous system and the musculoskeletal system[28]. A previous study has shown that using the opposing directions of acupuncture (following the meridian trajectory or in the inverse direction) at LI4 (Hegu) caused different therapeutic effects in terms of the recovery of central facial palsy[29]. Furthermore, a safety analysis showed that both acupuncture directions at GB20 (Fengchi) were safe among patients with posterior circulation ischemia vertigo[10].

There are several manipulations used in acupuncture. The basic motions include lifting, thrusting, and twirling. After needle penetration, needle manipulation is believed to reinforce acupuncture stimulation, and the manipulation frequency is a vital parameter. Recent studies have found that different acupuncture manipulation frequencies exert effects via different mechanistic pathways. An animal experiment showed that[20], compared with manual acupuncture of twice per second, a higher acupuncture twirling frequency (four times per second) had a stronger analgesic effect. To investigate the analgesia mechanism, the primary sensory afferent neuron type was examined and revealed that an acupuncture twirling frequency of four times per second activated C-fiber neurons, while that of twice per second stimulated A-fiber neurons.

After needle penetration and acupuncture manipulation, the duration of retention of the needle is another essential aspect of acupuncture therapy. Considering clinical feasibility, the retention time usually ranges from 10 minutes to 60 minutes[30]. The disease type is a vital factor that affects the retention time. For example, in a study of different acupuncture retention times in Knee osteoarthritis(KOA) patients, those who received 45-minute retention after needle penetration showed a greater clinical improvement than those with a retention time of 30 minutes[31]. A functional digestive disease study showed that, after needling at GB34 (Yanglingquan) in chronic cholecystitis patients, a 40-minute retention yielded a greater effect in reducing the high-tension state of the gallbladder than no needle retention[32].

In terms of acupuncture treatment sessions, a few studies have used different numbers of treatment sessions for comparison. However, by analyzing individual acupuncture studies related to a similar disease, we found that the number of treatment sessions influenced the acupuncture effects directly. In 2014, a clinical study of acupuncture for chronic KOA showed that after 8 to 12 sessions of treatment, there was no significant difference between the acupuncture group and the sham acupuncture groups[21]. In contrast, another study performed in 2019 proved that 24 sessions of electroacupuncture had significantly different effects than sham acupuncture in terms of reducing pain and improving KOA patients' function[22]. These three studies have proven that different number of acupuncture sessions can lead to contrasting results. The existing evidence in analgesia studies has proven that an adequate number of acupuncture sessions underlies the therapeutic effect[33]; however, the optimal number of acupuncture sessions needs to be explored further.

These previous studies have typically focused on a single acupuncture manipulation parameter, and revealed its dosage relationship with acupuncture effects. In clinical application, however, acupuncture therapy is a comprehensive operation involving multiple manipulation parameters. Hence, it is essential to conduct a study of combined manipulation parameters. Previous studies have reported using a combination of different acupoints and needle manipulation frequencies, needle retention time, and needle manipulation frequency[34]. In animal studies, we chose needle manipulation frequency (once per second, twice per second, three times per second) and needle retention time (5 seconds, 60 seconds, and 180 seconds) as intervention variables in middle cerebral artery occlusion model rats, comparing the combination effects in nine groups. The results indicated that the most powerful factor influencing the acupuncture

effect is the retention time, while the optimal parameters were a manipulation frequency of three times per second with a 60-second retention[35]. Additionally, this study showed that the interaction between needle manipulation frequency and needle retention time altered the acupuncture effect. Considering these aspects, future studies could focus more on the complex acupuncture manipulation parameter combinations.

De qi response

In the traditional Chinese medicine theory system, *qi* is the fundamental material of the human body, providing energy for functional activity. Interventions from outside, such as acupuncture, exert effects by regulating the disordered state of *qi*. *De qi* is a classic term in traditional Chinese medicine, representing adequate acupuncture stimulation. A *de qi* response is a manifestation of *qi* regulation and is presented as an intensified sensation in some acupuncture treatments, such as body acupuncture[36]. It should also be noted that in other acupuncture therapies, such as abdominal needling, floating needling, and wrist and ankle needling, a *de qi* response can present as no sensation[37]. The *de qi* response includes the response of patients after receiving acupuncture, and the sensation of the acupuncturist after conducting the acupuncture operation. Generally speaking, the *de qi* response refers to the patient's subjective feelings after receiving acupuncture, such as experiencing aching, numbness, dullness, heaviness, radiating, and spreading feelings. The various *de qi* responses are induced *via* different mechanism pathways.

The *de qi* response is induced by stimulating the skin and subcutaneous tissue using different acupuncture manipulations[38], it affects the acupuncture effect in the following four aspects. First, the local initial effect of acupoint: After needle penetration, the manipulation of the needle body reinforces the stimulation of the needle tip on connective tissue, vascular tissue, nervous tissue, and muscular tissue around the acupoint area. Different *de qi* sensations are evoked by needle tip stimulation on different tissues, which triggers different sensory receptors, such as muscle spindles, tendon organs, free nerve endings, joint capsules, and Pacinian corpuscles[39]. Second, the signal conduction effect: The activated receptors transform acupuncture mechanical stimulation into an electrical signal, which is conducted by different afferent fibers, including Aδ fibers, Aβ fibers, and C fibers, resulting in the *de qi* sensations in the cerebral cortex[40]. The central neural integration effect is the third part, which generates different *de qi* sensations. For instance, taking advantage of neuroimaging technology, functional magnetic resonance imaging examination revealed that there was a significant difference in the eigenvector centrality between participants who received acupuncture with or without *de qi* response[41]. During acupuncture, intensified manipulation of the needle strengthens the mechanical stimulation, influencing the metabolism of K^+, Ca^{2+}, and Na^+ and the release of 5-hydroxytryptophan, substance P, and histamine around the acupoint[42]. These active factors have an impact on the neuro-endocrine-immune network, which provides the structural and functional basis for acupuncture effect[43]. The neuro-endocrine-immune network is the fourth part. In the dose–effect relationship, the *de qi* sensation represents the dosage of acupuncture stimulation, and changes in the stimulation alter the therapeutic effects by activating different acupoint tissue, signal pathways, central neural integration, and neuro-endocrine-immune network.

In studies of the dose–effect relationship of acupuncture, it is difficult to define the minimal acupuncture "dosage". The *de qi* response offers a solution to this conundrum, because it can reflect the minimal acupuncture stimulation dosage to evoke a therapeutic effect. In a comparison of a group receiving standard Xingnao Kaiqiao acupuncture therapy and showing the *de qi* response to a similar acupuncture group without a *de qi* response, a previous study found different functional connectivity characteristics in the motor area of post-stroke patients[41]. A systematic review that used the *de qi* response as the standard for acupuncture dosage found that a higher acupuncture dosage was related to better clinical outcomes in KOA patients[9]. Therefore, the *de qi* response is an important standard for measuring whether the effect is adequate for the treatment demand.

However, the *de qi* response is a qualitative description. To evaluate the *de qi* response accurately, and to analyze the co-relationship among *de qi* response, acupuncture dosage, and treatment effect, there is a need for an instrument for evaluating the *de qi* response. Currently, various assessment scales for the *de qi* response are applied, which include the Southampton Needling Sensation Questionnaire, the Acupuncture Sensation Scale, the Massachusetts General Hospital Acupuncture Sensation Scale, and the Subjective Acupuncture Sensation Scale [44], which provide a visualized alternation for further study.

Nonspecific factors influencing the dose–effect relationship

Comparison selection

The control group should be chosen to reveal the real effects of different acupuncture dosages; thus, other interventions should be consistent with those of the treatment group, except for the acupuncture dosage. In studies of the acupuncture dose–effect relationship, the comparison should therefore depend on different acupuncture dosages. There are two mainstays of the comparison set, one is the comparison of different acupuncture dosages, and another is the comparison between a certain acupuncture dosage and the placebo acupuncture or no treatment (including the waiting list)[45]. For the former type, the variables of control groups can include single or multiple acupuncture manipulation parameters as we mentioned in the *Acupuncture manipulation parameters* section. While for the latter, the stimulation type and stimulation dosage of placebo acupuncture are vital factors influencing the dose–effect relationship. According to clinical studies and systematic review analysis, the effective power of acupuncture varied when it was compared with different comparisons such as no treatment group/waiting list group, sham acupuncture, and different types of sham acupuncture (non-penetrating needling, superficial needling, and deep needling at non-acupoints)[46]. An improper comparison with

a therapeutic effect might cover the real effect of acupuncture, and affect the conclusion in the study of the dose–effect relationship. Hence, the control intervention should be considered cautiously.

Blinding procedure

Several studies have demonstrated the placebo effects of acupuncture operation, particularly in analgesia studies[47]. However, evidence-based studies have validated that acupuncture has superior effects as compared to sham acupuncture[48–49], declaring that the acupuncture effects cannot be explained simply by placebo effects. Using a blinding procedure is a powerful way to reduce bias arising from the co-intervention of clinicians and participants, and to minimize placebo effects[16]. Given the potential placebo effects, which might amplify the real effects of acupuncture, the introduction of an appropriate blinding procedure is indispensable. Particularly, in a study of the acupuncture dose–effect relationship, the use of an improper blinding procedure might cause exaggerated effects, leading to inaccurate optimal dosage parameters. Due to the operational characteristics of acupuncture, it is difficult to blind the acupuncturist. Thus, the blinding procedure only relates to the participants, the outcome assessor, the data manager, and the statistician. Among these, the blinding of the participant is the basis of the blinding procedure.

Currently, there are three types of sham acupuncture used in blinding the participants. In terms of the needle type, a non-penetration needle is applied to simulate the acupuncture procedure. For example, both the classic Streitberger needle and the Park sham device contain a pad between the skin and the needle as well as a blunt needle tip, which prevents needle penetration[50–51]. For acupuncture manipulation, one alternative is superficial acupuncture. It maintains similarity to the acupuncture procedure, except for the needle depth. To reduce operation bias, a depth of 2 to 5 mm, which is above the muscular tissue, is typically used as the superficial acupuncture depth[52]. For acupoint selection, non-acupoints and non-meridian points without therapeutic effects are practicable approaches. This approach is highly consistent with true acupuncture in the needling procedure, and the penetration operation is acceptable for patients.

In the acupuncture dose–effect relationship study, the above blinding procedures can be used to accomplish blinding of the participant, but not that of the acupuncturist. Recently, auxiliary devices have provided approaches for double-blinding (both participant and acupuncturist). Using electroacupuncture, block of the current is a practical way to achieve double-blinding[53]. To ensure a blinding procedure, the combination of several procedures can be used, such as the non-penetration at non-acupoints with current-block electroacupuncture[16]. Moreover, to minimize the placebo effects, during the acupuncture operation, the acupuncturist could reduce interaction with participants. Meanwhile, in the dose–effect relationship study, participants in different groups receive acupuncture with different manipulation parameters, causing various needle senses in participants. Given the difficulty of performing the blinding procedure in participants who are with acupuncture treatment experience, it is necessary to select acupuncturists with greater practice experience who can conduct a better manipulation in acupuncture and sham acupuncture operations. For the outcome selection, the objective index is recommended since it can be less likely influenced by the placebo effects[47].

Patient's expectancy

Patient expectancy is one of the nonspecific factors influencing the acupuncture effect, it refers to the anticipation of patients about their treatment, response, outcome, and other reactions during the trial[54]. It is affected by the patient's treatment experience, the interaction between the patient and clinician, and the subjective perception of the patient during the trial[55]. According to a literature study, there are two prototypical types of patient expectancy[56]. "Outcome expectations" reflect patients' prognostic feelings about the therapeutic effects, and "Treatment expectations" suggest patients' personal beliefs about their interaction with the therapist, their feeling after receiving the treatment, the treatment duration, and treatment consistency[57–58].

A high-level positive expectancy might cause a placebo effect, while a negative expectancy, such as fear, might inhibit the analgesic effect of acupuncture[59]. Given the interaction between acupuncturists and patients, a positive expectancy might amplify the therapeutic effects[16]. On the other hand, some research presented the opposite conclusion, indicating that the treatment outcomes were inconsistent with patients' preferences for acupuncture[60]. Therefore, in the study of the acupuncture dose–effect relationship, the homogeneity of outcome expectations and treatment expectations among groups might cause expectation effects. To solve this problem, one practicable way is to take the expectation degree as a stratification factor in randomization. By balancing patient's baseline characteristics, the outcome expectation effects can be reduced. Another way is to minimize the treatment expectations, which requires the therapist to maintain uniformity in the acupuncture operation and communication with participants during the trial.

Ethics and compensatory acupuncture

In a clinical study, ethical approval is a guarantee of the safety of and benefits to participants. Considering the study of the acupuncture dose–effect relationship, participants in groups of different acupuncture dosages might obtain different therapeutic effects; thus, compensatory treatment is necessary. Currently, compensatory treatment includes acupuncture treatment, conventional treatment, or standard treatment[61]. For the study of the acupuncture dose–effect relationship, compensatory treatment can be acupuncture therapy at the optimal therapeutic effect parameters. The time point of compensatory treatment starts after the observation period of intervention or the follow-up stage. Another feasible way to protect participants' benefits is to provide healthcare or give health education[62]. To reduce bias rising from different interventions among groups, conventional treatment, standard treatment, or education treatment should maintain consistency throughout the trial.

Discussion

The acupuncture dose–effect relationship is a complex research question, for both "dose" and "effect" are associated with multiple factors. In this article, we summarized the vital methodological strategies in studies of the acupuncture dose–effect relationship. By analyzing factors that influence acupuncture dosage and effect, we offered practical suggestions according to current issues. Considering different research objectives and study procedures, we have offered advice for studies of the dose–effect relationship of single acupoints and acupoint combinations. Our suggestions might facilitate the design of future studies on acupuncture dosage and effect, and may establish a methodological system for evaluating the acupuncture dose–effect relationship. In addition, clarification of a specific "dose" has great significance in acupuncture treatment, as it is not only associated with the evaluation of therapeutic effect, but also influences health economics[63]. In some chronic diseases, such as musculoskeletal pain, a sufficient treatment course is required to achieve therapeutic effect[64]. Patients with insurance benefits are more likely to complete the full course of acupuncture treatment. With the expansion of health insurance[65], the optimal dosage needs to be defined to provide the basis for policymaking[66].

Current evidence has proven that this relationship between acupuncture dosage and effect is not a simple linear relationship. Besides methodological problems in study design, how to define the dosage and effects qualitatively is an unavoidable challenge. Recently, the combination of multidisciplinary fields has provided modern technological support. In the modern medicine system, acupuncture technology is considered an extraneous mechanical stimulation[67]. Through needle stimulation, acupuncture evokes electroneurographic signals and induces exciting conduction. Neural pathways have been proven to be crucially involved in the mechanism underlying the effects of acupuncture[68–69]. Based on these mechanisms, researchers who focus on the manipulation of acupuncture have proposed the hypothesis of the connective tissue pathway[70], which proposes that, after performing acupuncture manipulation, such as twirling, the needle tip is entwined in the connective tissue beneath the acupoint. Reinforcement of acupuncture manipulation results in the deformation of collagenous fibers, evoking the mechanical signaling pathway that is conducted via the fascia network[71–72]. Combining advanced technology of biology and mechanics, an acupuncture parameter collection system is applied in manipulation studies, which records and analyzes the manipulation parameter characteristics. In this way, the acupuncture manipulation can be recorded as quantified data, providing the possibility of accomplishing an acupuncture network system in terms of the acupuncture dose–effect level.

Multiple evidence-based studies have validated that the dose–effect relationship of acupuncture alters the therapeutic effects of acupuncture and the mechanistic pathways, providing the basis for an acupuncture dose–effect relationship. Using experimental research, the dose–effect relationship of acupuncture has been revealed on different levels, such as the mechanism of acupoint activation, and conduction between the acupoint, meridian, and the body. Recent studies have illustrated the possible mechanism underlying the acupuncture dose–effect relationship in terms of neural electrophysiology and neuro-endocrine pathways[73]. However, most studies of the effect mechanistic pathways of acupuncture remain in a preliminary stage, and further systematic investigations are required.

Additionally, this review had some limitations. First, this study analyzed the core challenges and offered advice in terms of acupuncture dose–effect study design, but other aspects of trial design, such as randomization, sample size estimation, and outcome selection are not fully illustrated. The methodological problems were selected according to the existing puzzles of acupuncture dose–effect studies. Since the methodological system for studying acupuncture dose–effect relationships is in a preliminary stage, further studies could consider integrating such a system. Second, this study mainly focused on a RCT design and experimental research. For design of trials of the acupuncture dose–effect relationship in other study types, further exploration is required. Third, although the research topic in this review was acupuncture treatment, the dose–effect relationship should also be investigated in other traditional Chinese medicine external therapies, such as moxibustion. Considering that both acupuncture and moxibustion play a role by applying external stimulation to the body, the stimulating dosage is a core factor influencing therapeutic effect. A recent study has proven the dose-dependent effect in moxibustion therapy[74], but further studies should highlight the significance of the dose–effect relationship in these therapies.

Conclusion

The acupuncture dose–effect relationship is a complex research question that involves various factors. To date, studies have proven that acupoint selection, needle depth, needle twirling frequency, needle direction, needle retention time, and treatment sessions can influence acupuncture effects. However, acupuncture therapy is complicated, and the mechanism underlying its dose–effect relationship is not yet fully illustrated. Taking advantage of modern technology, further studies can explore the mechanistic pathways of this relationship.

Our perspectives offer insight into the factors related to acupuncture dosage and effect, including specific influencing factors (acupoint selection, acupuncture manipulation parameters, *de qi* response) and nonspecific influencing factors (comparison selection, blinding procedure, patient's expectancy). Further studies need to be conducted to establish a methodological system and to provide systematic evidence on the acupuncture dose–effect relationship.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Boxuan Li conceived and wrote the manuscript. Menglong Zhang and Ngaenklangdon S helped with the figure and drafted the manuscript. Hailun Jiang, Weiming Zhu, Bifang Zhuo, Chenyang Qin, Yuanhao Lyu, Yuzheng Du, Shizhe Deng, and Zhihong Meng revised the manuscript. All authors have read and approved the final manuscript.

Ethical approval of studies and informed consent

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