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Original Paper

Efficacy of Acupuncture for Prurigo Nodularis: A Protocol for Systematic Review and Meta-analysis

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Abstract

Background*: Prurigo nodularis (PN) is a chronic inflammatory skin disease characterized by severe pruritus, significantly impairing patients' quality of life and work capacity. Acupuncture has emerged as a promising therapeutic option, with a growing body of research demonstrating its notable efficacy in treating this condition. However, the mechanisms involved remain unclear, and current evidence lacks integration to help clinical decisions. This study initiates the first systematic evaluation through meta-analysis to assess acupuncture's therapeutic value for PN.*

Methods*: Authors will systematically search the randomized controlled trial (RCT) literatures involving acupuncture for treating PN from PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (WOS), China National Knowledge Infrastructure (CNKI), China Biomedical Literature Database (CBM), Wanfang database, China Scientific and Technology Journal Database (VIP). We will define the Worst Itch Numeric Rating Scale (WI-NRS) and the Investigator's Global Assessment (IGA) as the primary outcomes, total effective rate, quality of life score (e.g., Dermatology Life Quality Index), adverse reactions caused by acupuncture will be regarded as the secondary outcomes. RevMan v.5.3 software will be used for the purposes of screening literature, gathering data, analyzing data, and synthesizing data. Additionally, authors will assess the risk of bias in all included studies using the Cochrane Collaboration's tool for risk of bias assessment.*

Results*: The protocol for the meta-analysis will systematically evaluate the efficacy of acupuncture in treating PN.*

Conclusion*: The conclusion of this protocol will provide evidence regarding the efficacy of acupuncture in treating PN, and establish a foundation for future acupuncture treatments.*

Trial registration*: PROSPERO registration number: CRD420261325566*

Ethics and dissemination*: As this study synthesizes existing data without involving individual patient information, ethics committee approval was exempted. The findings will undergo peer-reviewed*

publication and international conference presentation to ensure knowledge dissemination.

Keywords

acupuncture, prurigo nodularis, meta-analysis, protocol

1. Introduction

Prurigo nodularis (PN) is a highly pruritic chronic inflammatory skin disorder characterized by symmetrically distributed pruritic nodules on the limbs and trunk, often accompanied by pain, burning, and tingling sensations. Clinically, it is defined by the presence of numerous, usually symmetrical, hyperkeratotic and excoriated papules and nodules (Zeidler et al., 2018). According to a German study, PN has a prevalence of 0.1% and is more common in the elderly, with a higher incidence observed in females (Ständer et al., 2020). Furthermore, individuals of African American descent with atopic eczema tend to present with a greater number of PN lesions compared to other racial groups (Vachiramon et al., 2012). Pruritus associated with PN is recognized as one of the most severe forms among chronic pruritic conditions, and the intensity of PN-related pruritus profoundly impairs patients' quality of life, contributing to sleep disturbance, as well as elevated rates of anxiety and depression (Kwatra, 2022; Steinke et al., 2018). A study showed that among the patients with PN, 45.6% were diagnosed with anxiety, and 16.4% were diagnosed with major depressive disorder (Aggarwal et al., 2021). It has been reported that PN is associated with various comorbid conditions, including atopic dermatitis (Chalupczak et al., 2026), systemic and neurological disorders (Zeidler et al., 2018), chronic kidney disease (CKD) (Kim et al., 2022), diabetes mellitus (Tseng et al., 2015), as well as infectious diseases (notably HIV) (Magand et al., 2011) and psychiatric disorders (Ständer et al., 2007). Current evidence indicates that the development of prurigo nodularis centers on immune-neural dysregulation, driven by specific inflammatory cytokines (IL-4, IL-13, IL-17, IL-22, IL-31) and neuropeptides (e.g., substance P and calcitonin gene-related peptide). Immune molecules released from T cells elevate systemic inflammation, which is increased in PN patients. Activated inflammatory cells degranulate and release neurotoxins and nerve growth factor, potentially contributing to neuronal hyperplasia in the dermis of individuals with PN and neural sensitization (Liao et al., 2024). Furthermore, the inaugural genetic study conducted on PN patients revealed a distinct polygenic risk score, suggesting a combination of an underlying genetic predisposition and environmental triggers in the etiology of the disease (Vasavda et al., 2023).

Owing to the unclear pathogenesis of PN, existing therapeutic options provide suboptimal relief for pruritus and have limited success in resolving nodules. The first medication approved by the U.S. Food and Drug Administration (FDA) for prurigo nodularis (PN) is dupilumab, an IL-4Rα inhibitor that blocks signaling through both IL-4 and IL-13. Furthermore, several other agents are under development, including nemolizumab, ruxolitinib, abrocitinib, and povorcitinib. The first medication approved by the U.S. Food and Drug Administration (FDA) for prurigo nodularis (PN) is dupilumab, an IL-4Rα inhibitor that blocks signaling through both IL-4 and IL-13. Furthermore, several other agents are under

development, including nemolizumab, ruxolitinib, abrocitinib, and povorcitinib (Hamilton et al., 2014; Liao et al., 2024). In addition to these targeted therapies, PN management encompasses a range of other treatment modalities. These include topical corticosteroids (Saraceno et al., 2010), topical anesthetics (Kwatra, 2022), capsaicin (Ständer et al., 2001), and ultraviolet (UV) therapy (Hammes et al., 2011), as well as systemic agents such as gabapentin (Gründel et al., 2020), μ-opioid receptor antagonists (Yook & Lee, 2024), and antidepressants (Bahloul et al., 2024). However, phototherapy and topical treatments are sufficient for only a small subset of PN patients, and systemic agents are frequently associated with various unpleasant side effects (Kwatra, 2022; Nwankwo et al., 2024; Pillinger et al., 2023; Streicher & Bilsky, 2018). Consequently, the discovery of a safe, effective, cost-effective, and well-tolerated regimen for PN represents a major unmet need.

Nevertheless, beyond the aforementioned approaches, acupuncture emerges as a viable alternative in the treatment of PN. As a pivotal element of traditional Chinese medicine, acupuncture not only occupies a prominent position in the treatment of skin diseases but also serves as an indispensable therapy in the management of PN within China (Ma & Sivamani, 2015). Acupuncture, used independently or as an adjunctive therapy, has been reported in clinical observations to ameliorate pruritus and inhibit the development of new cutaneous lesions in individuals with prurigo nodularis (Sun et al., 2018; Tang et al., 2021; Wu & Dong, 2021; Zhang et al., 2015). However, these studies were limited by small sample sizes and heterogeneous outcome measures, highlighting the need for a systematic synthesis of evidence. The efficacy of this treatment modality for PN remains uncertain, as no systematic review or meta-analysis has been conducted to comprehensively evaluate its impact. Consequently, conducting a systematic and rigorous assessment of the effectiveness of acupuncture in treating PN holds significant importance.

2. Methods

2.1 Study Registration

We will report in accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement (Shamseer et al., 2015). The study protocol has received formal registration through PROSPERO (International Prospective Register of Systematic Reviews) under the unique identifier CRD420261325566.

2.2 Inclusion Criteria for Study Selection

2.2.1 Type of Studies

All randomized controlled trials (RCTs) in English or Chinese to evaluate the efficacy of acupuncture on PN will be included. Other designs, such as animal experiments, case report, reviews and non-RCTs will be excluded.

2.2.2 Types of Participants

Patients who meet the diagnostic criteria of PN will be included in this study. There are no restrictions on gender, race, age, nationality, etc., but patients with severe underlying diseases (Basic metabolic

disorders, immunocompromised diseases, and major chronic consumptive diseases) will be excluded.

2.2.3 Types of Interventions

The interventions considered in this study must involve needle insertion at acupuncture points, and must be described as acupuncture. The practice of acupuncture incorporates diverse methods ranging from traditional needle manipulation to technologically enhanced approaches like electroacupuncture, along with specialized techniques such as scalp acupuncture and fire needle. This review will include trials in which acupuncture is used either alone or in combination with other therapies, provided that the same combination of therapies is administered to both the experimental and control groups. However, other methods of stimulating acupuncture points without needle insertion, such as moxibustion, laser stimulation, massage, or transcutaneous electrical nerve stimulation, will be excluded from this study.

2.2.4 Types of Comparator(s)/Control

For the control groups in this study, we will receive simulated interventions, encompassing placebo-based procedures (e.g., blunt-tip device application, shallow insertion at anatomical non-meridian sites) and equivalent alternative modalities. Additionally, routine care interventions such as functional exercise, and/or electrotherapy (e.g., ultrasound or short-wave therapy) will also be considered. However, studies that only compare acupuncture with other complementary and alternative therapeutics, will be excluded from this study.

2.2.5 Types of Outcome Measures

2.2.5.1 Primary outcomes

The primary outcome of this systematic review includes the Worst Itch Numeric Rating Scale (WI-NRS) and the Investigator's Global Assessment (IGA).

2.2.5.2 Additional outcomes

The additional outcome of this systematic review includes total effective rate; quality of life score (e.g., Dermatology Life Quality Index), adverse reactions caused by acupuncture.

2.3 Search Methods

From its establishment to January 2025, the following eight electronic databases will be searched, including PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (WOS), China National Knowledge Infrastructure (CNKI), China Biomedical Literature Database (CBM), Wanfang database, China Scientific and Technology Journal Database (VIP) to obtain RCTs in this regard. The language will be limited to English and Chinese. In Chinese database, Chinese characters with the same meaning will be used for literature retrieval. The specific search strategy for PubMed is shown in Table 1.

Table 1. Search Strategy Used in PubMed Database

No.	Search items
#1	randomized controlled trial as topic [mh]
#2	randomized controlled trial [pt]
#3	controlled clinical trial as topic [mh]
#4	randomized [tiab]
#5	controlled [tiab]
#6	clinical trials [pt]
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	humans [mh]
#9	#7 and #8
#10	prurigo [mh]
#11	prurigo nodularis [tiab]
#12	nodular prurigo [tiab]
#13	#10 or #11 or #12
#14	acupuncture therapy OR electroacupuncture therapy [mh]
#15	(acupuncture OR acupoint OR electro-acupuncture OR scalp acupuncture OR auricular acupuncture OR warm needling OR fire needle) [tiab]
#16	#14 or #15
#17	#9 and #13 and #16

2.4 Study Selection

Two completely independent reviewers (SMY and SYH) will evaluate the titles and abstracts of all studies separately to exclude irrelevant or duplicate literature. After the initial screening, they will carefully read the full text to determine whether the relevant research will eventually be included in the protocol. In the full-text assessment phase, inter-reviewer disagreements arising from dual independent screening will be resolved through discussion. A third reviewer (XHL) will participate in the extraction and discussion if the first two have controversial information. The specific process of the study will be shown in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A flowchart illustrating this study is shown in Figure 1.

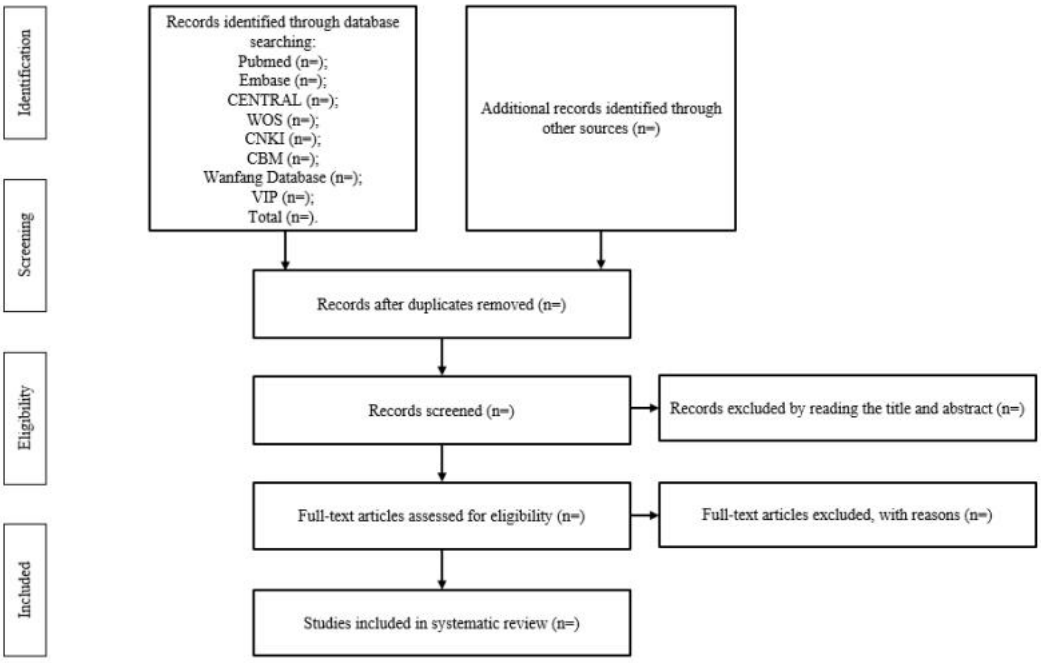

Figure 1. Flow Diagram of the Study Selection Process

2.5 Extraction

A predefined data template with the following information will be provided, containing participants, general information, interventions, controls, outcomes, adverse events, and other information. Three investigators (SMY and SYH) will independently extract and encode the obtained data according to the above template, and these data will also be examined.

2.6 Dealing with Missing Data

If necessary, the original author of the literature will be contacted to obtain the original data. In the face of unavailable data, if there is continuous loss of data, MD and SD values will be recalculated for further analysis (Kambach et al., 2020). Secondly, the estimation transformation will be carried out according to the existing data, and it will be regarded as the obtained data. If there is a potential impact on the final result, it will be pointed out in the discussion.

2.7 Risk of Bias Assessment

Employing intention-to-treat (ITT) analysis principles, three principal investigators (SMY, SYH) will independently conduct a critical appraisal of methodological rigor using the Cochrane ROB2 tool (Minozzi et al., 2022). The assessment will focus on five key domains of bias: adequacy of the randomization process, adherence to intended interventions, completeness of outcome data, objectivity of outcome measurement, and selection of the reported result (Sterne et al., 2019). Concurrently, evidence certainty will undergo hierarchical calibration through the GRADE framework via GRADEpro GDT, implementing tripartite confidence stratification (high/moderate/low) with adjudication thresholds set at $\kappa \geq 0.8$ inter-rater consistency indices. This dual-phase validation

architecture, integrating standardized bias profiling with evidence-to-decision analytical protocols, ensures methodological transparency and synthesizes evidentiary robustness for subsequent meta-analytic interpretations.

2.8 Quality of Evidence

Researchers will use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to independently evaluate the quality of evidence. The assessment will be graded as high, Moderate, low, and very low (Puhan et al., 2014).

2.9 Data Synthesis

The data will be analyzed utilizing RevMan V.5.3. Dichotomous data will be presented in terms of relative risk, while continuous variables will be depicted as mean difference, both accompanied by 95% confidence intervals (CIs). In cases where the units of continuous variables differ, standardized mean difference along with 95% CI will be employed. Statistical significance is determined when $p<0.01$.

2.10 Assessment of Heterogeneity

To determine the appropriate model for data synthesis, we will use the I^2 test to assess heterogeneity. If the I^2 test result is less than 50%, we will use the fixed-effects model for data synthesis. If the I^2 test result is between 50% and 75%, we will use the random-effects model. If the I^2 test result is higher than 75%, we will explore possible reasons for the high heterogeneity from both clinical and methodological perspectives. We will provide an explanation for the observed heterogeneity and may conduct a subgroup analysis to further investigate the sources of variation.

2.11 Assessment of Reporting Bias

If an adequate amount of studies are incorporated, the Egger test will be employed to evaluate potential reporting biases.

2.12 Subgroup Analysis

If the data are available, the researchers will conduct subgroup and sensitivity analyses, taking into account the characteristics of the trial participants and variations in acupuncture treatment. The planned subgroup analyses will encompass age, distinct acupuncture stimulation techniques, the control group, and the severity of PN. In the event that significant heterogeneity is detected during the study, we will undertake subgroup or sensitivity analyses to pinpoint the underlying cause. If not, we will present a descriptive summary of the findings.

2.13 Sensitivity Analysis

When notable heterogeneity arises, we will undertake a sensitivity analysis, examining diverse factors such as study designs, age variations, gender distinctions, study quality, length of treatment, treatment intervals, and characteristics of heterogeneity.

2.14 Ethics and Dissemination

As this investigation did not collect any personally identifiable patient data, formal ethics committee review was deemed unnecessary under institutional guidelines. The protocol outcomes will undergo peer evaluation prior to journal publication.

3. Discussion

PN is a chronic, inflammatory skin condition manifesting as severely pruritic, hyperkeratotic nodules with a predilection for the trunk and extremities (Manjunath et al., 2025). Evidence shows that PN imposes a multifaceted burden on patients, encompassing intense pruritus, sleep disturbances, reduced social functioning attributable to lesion appearance, and an increased incidence of anxiety and depression, resulting in a profoundly negative impact on quality of life (Brown & Khachemoune, 2024). Current therapeutic options, including topical corticosteroids, systemic immunosuppressants, and phototherapy, often offer limited efficacy and are associated with adverse effects. The novel agent Dupilumab, while effective, is relatively costly. This situation highlights an urgent need for alternative treatment modalities.

With its versatility in application, favorable safety and economic profile, acupuncture has been established as a therapeutic intervention with notable therapeutic effects for PN (Wu & Dong, 2021). Consequently, we aim to undertake the first comprehensive systematic review and meta-analysis to assess the effectiveness of acupuncture in managing PN. As the first systematic review and meta-analysis protocol specifically focused on acupuncture for PN, this study pioneers the integration of Eastern and Western evidence. Our rigorous methodology—incorporating PROSPERO pre-registration, dual-independent screening, and GRADE evidence profiling—establishes a benchmark for future research in traditional medicine.

However, the findings should be interpreted with caution due to three primary limitations. Firstly, the existing evidence base is relatively weak; both the volume of theoretical research in this field and the number of clinical randomized controlled trials remain limited. Secondly, current studies often exhibit methodological flaws; for instance, literature searches are hindered by language barriers, and there is a significant lack of high-quality randomized controlled trials and evidence-based medicine that meet our inclusion criteria. Thirdly, technical heterogeneity and inconsistent definitions of efficacy complicate cross-trial comparisons despite our predefined subgroup analyses. Variations in acupuncture point selection during treatment, differences in needle retention duration, and inconsistencies in manipulation techniques all contribute to an increased risk of performance bias. We anticipate that the findings of this study will prompt greater interest among researchers and experts in related fields, and provide more comprehensive evidence and support for the use of acupuncture in treating PN.

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