Topical anticholinergic medications for primary hyperhidrosis: A protocol for systematic review and meta-analysis

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ABSTRACT

Introduction
Primary hyperhidrosis (PHH) is a chronic condition characterized by excessive sweating. Several topical anticholinergic agents have been developed, but the evidence for the efficacy and tolerability of changing medication pathways of anticholinergics for PHH is limited.

Methods and analysis
PubMed, the Cochrane Library, Embase, the Web of Science, and the Cochrane Central Register of Controlled Trials will be searched from inception to March 2022 for studies that may be eligible for inclusion. Randomized controlled trials (RCTs) of PHH treated by topical anticholinergic drugs will be included. The primary outcomes include severity of hyperhidrosis measured quantitatively, the Hyperhidrosis Disease Severity Scale (HDSS) score or the proportion of subjects with a minimum 2-grade improvement from baseline in HDSS, the Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) score and Dermatology Life Quality Index (DLQI). The secondary outcomes focused on safety and tolerability. Study selection, data extraction and assessment of risk of bias will be performed by two investigators independently. Data synthesis will be performed with RevMan 5.4 software.

Ethics and dissemination
Ethical approval will not be needed in this review due to no data are involved in patient’s information and privacy. The results will be published and diffused in a peer-reviewed journal or relative conferences.

Keywords: Primary hyperhidrosis, anticholinergic drugs, topical, systematic review

Strengths and limitations of this study
This systematic review will be the first to evaluate the efficacy and safety of topical anticholinergic agents in the treatment of PHH.

Different inclusion criteria between studies and different skin sites where drugs applied may lead to clinical heterogeneity, which will be explored in the subgroup
This study will also focus on evaluating systemic and topical safety and tolerability of topical application of anticholinergics.

INTRODUCTION

Hyperhidrosis (HH) refers to a chronic disease in which exorbitant sweating exceeds the physiological requirements for maintaining internal temperature regulation\(^1,2\). HH is characterized by excessive local or systemic sweating due to exocrine sweat gland hyperfunction\(^3,4\), commonly found in areas such as axillae, palms, soles, and face\(^5,6\). Hyperhidrosis is divided into primary hyperhidrosis (PHH) and secondary hyperhidrosis based on whether there is an underlying disease or drug use\(^2,7\). The prevalence of HH ranges from 1% to 4.8%\(^8,9\), which is mostly seen in children and adults, and the average age of onset is 14-25 years\(^10\). Many of the discomforts associated with severe hyperhidrosis can interfere with daily life and even lead to social and work isolation\(^11-13\), with significant negative effects on the patient's daily activities, mental health, and professional behavior\(^14,15\).

The pathophysiology, diagnosis, and treatment of PHH are attracting wide attention. Perspiration is produced by the secretion of sweat glands innervated by cholinergic nerve fibers of the sympathetic nervous system\(^16\). Studies suggest that hyperactivity of cholinergic nerve fibers in sweat glands may lead to PHH\(^17\). In addition, excessive number or abnormal distribution of sweat glands may also be the cause of the disease\(^18\). The anterior cingulate cortex, which controls the response to emotional stimuli, also has a significant influence\(^19\).

Management of PHH includes systemic, local, psychological and surgical treatment\(^16\). Systemic therapies include oral anticholinergic drugs\(^20\), such as oxybutynin\(^21\). Topical treatment includes the use of alumina, which chemically blocks sweat ducts to reduce sweating\(^22\), as well as topical anticholinergic agents such as glycopyrronium bromide. Ion import at specific sites is usually the treatment choice for HH of the palms and soles, but long-term maintenance treatment is required\(^23\). Botulinum toxin type A (Botox, approved by FDA in 2004\(^6\) and subsequently by several countries\(^24\)) is the first or second-line treatment option for axillary and plantar hyperhidrosis\(^25\). This toxin blocks cholinergic stimulation of sweat glands. Psychotherapy is beneficial in a few cases\(^26,27\). Surgery including local surgery and endoscopic thoracic sympathetic nerve resection can be considered when conservative treatment fails\(^7,28\).

However, these treatments have certain side effects or complications. Adverse reactions to oral anticholinergic drugs are obvious\(^29\), the most common symptom, dry mouth, often causes patients to stop treatment\(^30\). And studies have found that its efficacy decreases in long-term treatment\(^31\). Others such as skin irritation, pain, and burns caused by Ion import\(^32\), repeated injections of Botox\(^16\), and compensatory sweating after sympathetic nerve resection\(^33,34\).

Therefore, improving the tolerance of preparation has become the focus of research, especially the adjustment of oral preparation to external use\(^35\). Several topical anticholinergic drugs have been approved in recent years. Glycopyrronium Tosylate
(GT, Qbrexa™, a pre-wetting cloth containing 2.4% Glycopyrronium solution) reduces sweating by blocking the activation of acetylcholine receptors in peripheral sweat glands[15] and was approved by the FDA in 2018[36]. Topical Sofpironium bromide(ECCLOCK®, 5%) gel reduces sweat secretion by inhibiting local sweat gland M3 muscarinic receptor[37], approved in Japan in September 2020. In addition, topical preparation of GPB has aroused interest as a treatment option for PHH[38], and 1% GPB cream has completed the phase IIIa study[39]. A dermal preparation of Umeclidinium (UMEC) ammonium bromide is also under way[40].

Previous meta-analyses have assessed the efficacy and safety of oral anticholinergic agents (oxybutynin, methane bromide, glycopyrrolate, etc.) in the treatment of PHH and have shown that improved outcomes come at the expense of a large number of adverse events[5]. There are currently several topical anticholinergic agents on the market, and the evidence for efficacy and tolerability of a change in route of administration in the treatment of PHH has not been thoroughly evaluated. Therefore, literature review and meta-analysis are necessary to provide supporting evidence for current guidelines and more reliable evidence-based medicine references for clinical practitioners and researchers.

OBJECTIVE
This systematic review aims to combine current evidences on the efficacy and safety of topical anticholinergic agents in the treatment of PHH.

METHODS AND ANALYSIS
Study registration
This meta-analysis protocol follows the Preferred Reporting Items and Meta-analysis Protocol for Systematic Evaluation (PRISMA-P)[41] and the Manual for Systematic Evaluation of Cochrane Interventions. The PRISMA-P checklist is in the S1 Appendix. The protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO). The investigators will receive consistent training to ensure that they are familiar with the background, purpose, and methodology of the system's evaluation.

Eligibility criteria
Type of studies
Randomized controlled trials (RCTs) of PHH treated by topical anticholinergic drugs will be included. Completed trials published on the clinical trial registration platform will also be included. Quasi-randomized trials will be excluded.

Types of participants
Participants with a diagnosis of primary hyperhidrosis based on focal, visible, excessive sweating of at least 6 months in duration without apparent cause, at the same time, meeting two or more of the following conditions: (1) onset age of 25 years or younger, (2) bilateral and relatively symmetric distribution, (3) at least one episode weekly, (4) cessation of sweating during sleep, (5) impaired daily activities, (6) family
history of primary hyperhidrosis, will be included. And participants had to with a hyperhidrosis disease severity scale (HDSS) scores of at least 3 during baseline evaluation.

Patients with secondary hyperhidrosis will be excluded. And patients will be excluded if they had another concurrent cutaneous or subcutaneous disease, or if they had received any procedure or treatment that could interfere with drug activity.

**Type of interventions and controls**
RCTs comparing topical anticholinergics such as glycopyrronium tosylate, sofpironium bromide, umeclidinium with placebo will be included. Trials comparing the same type of anticholinergic drug but at different concentrations or different treatment duration will be considered as eligible. Trials involving combination therapy (eg, combination of topical and oral application of anticholinergics) will be excluded.

**Type of outcome measures**
Primary outcomes: (1) Severity of hyperhidrosis measured quantitatively (e.g. gravimetry, evaporimeter, and minor starch-iodine test). (2) the Hyperhidrosis Disease Severity Scale (HDSS) score or the proportion of subjects with a minimum 2-grade improvement from baseline in HDSS. (3) the Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) score. (4) the Dermatology Life Quality Index (DLQI).

Secondary outcomes: Safety and tolerability will be evaluated using the following outcomes: (1) Total number of patients who experienced treatment-emergent adverse events (TEAEs) such as blurred vision or mydriasis, dry mouth, urinary retention, constipation, anhidrosis, dizziness, headache, nasopharyngitis, etc. (2) Total number of patients experienced local skin reactions (LSRs), including burning, stinging, pruritus, edema, erythema, dryness, and scaling, etc. (3) Total number of patients experienced serious adverse events(according to the classification employed by the US FDA).

**Data sources and search strategies**
PubMed, the Cochrane Library, Embase, the Web of Science, and the Cochrane Central Register of Controlled Trials will be searched from inception to March 2022 for studies that may be eligible for inclusion. In addition, we will identify other studies that meet the criteria from the list of references included in the study. Clinical trial registries such as clinicaltrials.gov and WHO ICTRP will also be searched for ongoing or unpublished clinical trials.

The two investigators (DG and WZ) independently searched the literature, using a combination of medical subject heading (MeSH) terms and free-text terms, and designed a search formula for each electronic database, including "hyperhidrosis", "anticholinergic drugs", and "randomized controlled trials". There are no language restrictions in the search process. PubMed's search strategy is shown in S2 Appendix and will be modified to meet the needs of other databases.
Studies selection
The literature will be screened independently by two investigators (DG and WZ) according to pre-established inclusion and exclusion criteria. The search results were imported into Endnote X9.0 software and duplicated data were deleted. Read the titles and abstracts of studies independently to screen out irrelevant studies and records. The full paper will then be read, and non-randomized controlled trials, unqualified controls, and duplicate studies will be excluded. Any discrepancies in the screening process will be resolved by a third investigator (YS). The details of studies selection are summarized as a flow chart (Figure 1).

Data extraction and management
Two investigators (DG and WZ) will independently extract the data using standard Excel spreadsheets, including the first author, year of publication, the country, the research types, research design, baseline information for each group, intervention, and treatment time, outcome indicators, adverse reactions, etc. The extracted data will be cross-checked. If there is disagreement, it will be resolved by a third researcher (YS). When data is missing or difficult to reliably extract, authors will be contacted by mail for information.

Assessment of risk of bias
The Cochrane Risk Assessment of Bias Tool[42] will be applied by two investigators to assess the risk of bias of included RCTs independently. The assessment included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The criteria used to assess the risk of bias are "low risk", "high risk" and "unclear"[42]. Disagreement about the risk of bias was resolved by a third investigator (YS). A bias risk assessment chart will be generated to show the assessment results and details.

Statistical analysis
We will use Review Manager 5.4 software[41] (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) for data synthesis and statistical analysis. For dichotomous variables, relative risk (RR) and risk difference (RD), 95% confidence interval (CI), and P-value will be calculated. For continuous variables, mean difference (MD) or standard mean difference (SMD), 95% confidence interval (CI), and P-value will be calculated. And the random-effects model will be used. At the same time, the Q test and I² index will be used to assess statistical heterogeneity. When heterogeneity is significant (I²>50%), we will explore possible sources of heterogeneity firstly. Sensitivity analysis will then be performed as needed to account for heterogeneity and subgroup analysis or meta-regression will be performed to assess potential sources of heterogeneity[41]. Finally, if there is considerable heterogeneity cannot be solved, a systematic review of descriptive analysis will be performed.
Dealing with missing data
If there are missing data from included RCT studies, the investigators will attempt to contact the corresponding author of the study by email. If complete data is still not available, the study will not be included. The potential impact of missing data was assessed using sensitivity analysis and described in the results.

Subgroup analysis and sensitivity analysis
Subgroup analysis based on different drugs and different skin sites (forehead, axillae, palms, etc.) where drugs applied will be conducted. If there’s a significant heterogeneity, trials will be further classified to perform subgroup analysis after explored. Sensitivity analysis will be performed to evaluate the robustness of the results and to explore the source of heterogeneity.

Publication bias
When more than 10 studies meet the inclusion criteria, we will evaluate potential publication bias by drawing funnel plots and Egger tests.

Grading the quality of evidence
We will evaluate the evidence quality of the included studies according to The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[43], and the evidence quality GRADE is divided into four grades: high, moderate, low, and very low.

Patient and public involvement
No patients or the public will be involved in this study.

Ethics and dissemination
This protocol and the systematic review do not require ethical approval. The final report will be published in a peer-reviewed journal or at a relevant conference.

DISCUSSION
Although there are many therapeutic options for PHH, treatment plans should be individualized according to the actual situation of patients[35]. Clinical guidelines for PHH no longer recommend systemic therapy because of unacceptable adverse reactions to oral anticholinergic drugs in recent years[44]. Topical anticholinergic agents optimize existing therapies and are likely to replace systemic oral administration[17]. It is necessary then to comprehensively evaluate the existing evidence and conduct a meta-analysis on the efficacy and tolerability of anticholinergic drugs for external use in the treatment of PHH, hoping to draw conclusions that can benefit patients, clinicians, and researchers with primary hyperhidrosis.

CONFLICTS OF INTEREST
All authors declare that there is no conflict of interest related to the publication of the paper.

DATA AVAILABILITY STATEMENT
The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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