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Comparative Efficacy and Safety of Systemic Treatments for Cutaneous Leishmaniasis: A Systematic Review and Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

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 10 July 2025 and was last updated on 10 July 2025.

INTRODUCTION

Review question / Objective What is the comparative efficacy and safety of systemic therapies for cutaneous leishmaniasis, as evaluated through randomized controlled trials?

Condition being studied Cutaneous leishmaniasis (CL) is a parasitic disease caused by various species of the Leishmania genus, primarily transmitted through the bites of infected female phlebotomine sandflies. It is characterized by the development of skin lesions and ulcers, which can significantly affect the patient's quality of life and may lead to permanent scars. The disease is prevalent in many tropical and subtropical regions, including parts of Africa, Asia, and South America. Clinically, CL manifests as cutan
Clinically, CL manifests as cutaneous lesions that can vary in appearance, including papules, nodules, and ulcers, often accompanied by swelling of the surrounding tissue. If left untreated, lesions may become chronic and lead to secondary infections. While CL is not typically life-threatening, its physical and psychological impacts can be considerable, making effective treatment essential. Treatment options for cutaneous leishmaniasis include topical therapies, systemic therapies, and surgical interventions, with systemic treatments often being necessary for more severe or widespread cases. However, there is a variation in the efficacy and safety of these treatments, which highlights the need for systematic reviews and meta-analyses to guide clinical decision-making.

METHODS

Participant or population The review will focus on patients diagnosed with cutaneous leishmaniasis, specifically those who meet the following criteria:
Age: All age groups will be included, from children to adults, as cutaneous leishmaniasis can occur across different age demographics. Diagnosis: Participants must have a confirmed diagnosis of cutaneous leishmaniasis through clinical evaluation and laboratory confirmation, such as positive

identification of Leishmania parasites in skin biopsy specimens or other diagnostic methods.

Location: Participants will be drawn from regions endemic to cutaneous leishmaniasis, including but not limited to parts of the Middle East, Africa, Asia, and Latin America. Clinical Presentation: Participants may present with various forms of cutaneous leishmaniasis, including but not limited to single or multiple lesions, which may be acute or chronic in nature.

Treatment History: The review will consider both treatment-naïve patients and those who have previously undergone treatment for cutaneous leishmaniasis, as this may impact the outcomes and effectiveness of systemic therapies.

Intervention The review will evaluate the following systemic therapies for cutaneous leishmaniasis as the primary interventions:

Antimonial Compounds:

Sodium Stibogluconate (Pentostam): Commonly used as a first-line treatment for cutaneous leishmaniasis in many endemic regions.
Meglumine Antimoniate (Glucantime): Another antimonial agent widely used to treat various forms of leishmaniasis. Miltefosine:

An oral phospholipid treatment that has shown efficacy in various forms of leishmaniasis, including cutaneous leishmaniasis, and is gaining prominence due to its favorable oral administration route.
Amphotericin B:

Liposomal formulations of amphotericin B are being used for severe cases of cutaneous leishmaniasis and are noted for their effectiveness and safety profile compared to traditional formulations. Azoles (e.g., Itraconazole, Fluconazole):

These antifungal agents have shown potential in treating cutaneous leishmaniasis, particularly in cases unresponsive to other therapies.
Combination Therapies:

The review will also explore investigations involving combinations of systemic treatments, such as antimonials and azoles, to evaluate synergistic effects and improved efficacy. Adjunct Therapies:

Any additional treatments that may be used alongside systemic therapies, such as topical applications or immunotherapy, will also be noted, although the primary focus will remain on systemic interventions.

Comparator The review will include the following comparators for evaluating the efficacy and safety of systemic therapies for cutaneous leishmaniasis:

Placebo:

Randomized controlled trials (RCTs) that compare systemic therapies against a placebo treatment will be included to assess the true effect of the intervention without the influence of additional treatment effects.
No Treatment:

Studies that observe untreated patients or those who are receiving standard of care but not specific systemic therapies will be included to evaluate the benefit of active interventions compared to a watchful waiting approach.
Alternative Systemic Treatments:
Comparisons may also be drawn against other systemic therapies for cutaneous leishmaniasis, such as:
Antimonial compounds (e.g., Sodium Stibogluconate, Meglumine Antimoniate): When one antimonial agent is compared against another.
Miltefosine: Evaluating its effectiveness in relation to other systemic therapies.
Amphotericin B: When used in comparison to other treatments for efficacy and safety.

Topical Treatments:

While the primary focus is on systemic therapies, studies comparing systemic medications to topical options (like cryotherapy or topical paromomycin) may also be included for a broader understanding of treatment impacts.
Combination Therapy Control Groups:

Trials that investigate combinations of different therapies will be considered, especially when assessing the efficacy of one specific systemic treatment versus another combination.

Study designs to be included The review will include the following study designs to address the objective: Randomized Controlled Trials (RCTs):Studies that randomly assign participants to receive either systemic therapies or comparator interventions.The review will include the following study designs to address the objective:Randomized Controlled Trials (RCTs):Studies that randomly assign participants to receive either systemic therapies or comparator interventions.Cohort Studies:Well-designed

prospective and retrospective cohort studies that evaluate the efficacy and safety of systemic treatments for cutaneous leishmani.

Eligibility criteria Inclusion Criteria:
Population: Patients of all ages diagnosed with cutaneous leishmaniasis confirmed through clinical evaluation and laboratory tests.
Intervention: Studies evaluating systemic therapies, including antimonial compounds, miltefosine, amphotericin B, azoles, and combination therapies.
Comparator: Studies comparing systemic treatments against placebo, no treatment, and alternative systemic treatments.
Exclusion Criteria:
Non-systematic Reviews: Non-original research articles, such as editorials, commentaries, and narrative reviews.
Animal Studies: Studies conducted on animals or non-human subjects.
Incomplete Data: Studies lacking sufficient data on outcomes or interventions, making it impossible to assess efficacy or safety.
Duplicate Publications: Studies reporting on the same patient population or data set as other included studies.

Information sources PubMed; Web of Science; Scopus; Google Scholar.

Main outcome(s) The primary outcomes of the review will focus on the efficacy and safety of systemic treatments for cutaneous leishmaniasis, including:

Efficacy Outcomes:

Cure Rate: The proportion of patients achieving complete healing of lesions, defined as the absence of clinically visible lesions, measured at 3, 6, and 12 months post-treatment.
Lesion Size Reduction: The percentage reduction in the area of lesions measured at baseline and after treatment at specified follow-up intervals.
Safety Outcomes:

Adverse Effects: The incidence and types of adverse events reported, categorized as mild, moderate, or severe, during and after treatment. Monitoring periods will vary based on the study design but will typically include evaluations at the end of treatment and during follow-ups (1, 3, and 6 months).

Quality assessment / Risk of bias analysis The Cochrane Risk of Bias Tool will be used, which evaluates potential biases across several domains:
Random Sequence Generation: Assessing whether the allocation sequence was generated randomly.
Allocation Concealment: Determining if allocation to interventions was adequately concealed from participants and personnel.
Blinding: Evaluating whether participants and investigators were blinded to treatment allocation to minimize bias.
Incomplete Outcome Data: Reviewing how missing data were handled and whether there was a balance in losses to follow-up.
Selective Reporting: Checking for discrepancies between reported and unreported outcomes.

Strategy of data synthesis The synthesis of data in this systematic review will involve both qualitative and quantitative approaches, depending on the nature of the data collected from the included studies.

Descriptive Analysis:

A preliminary descriptive analysis will be conducted for all included studies. This will involve summarizing key characteristics such as study design, population demographics, interventions, comparators, outcomes measured, and duration of follow-up.
Qualitative Synthesis:

If there is substantial heterogeneity in the types of interventions or outcomes measured, a qualitative synthesis will be performed. This will involve a narrative summary of findings from the included studies, highlighting key themes and trends regarding the efficacy and safety of systemic treatments for cutaneous leishmaniasis.
Quantitative Synthesis (Network Meta-analysis):

If the data from the included studies are sufficiently homogeneous in terms of interventions and outcomes, a meta-analysis will be performed using random-effects or fixed-effects models, depending on the level of heterogeneity as assessed by statistical tests (e.g., I^2 statistic).

Subgroup analysis Subgroup Old World and New World.

Sensitivity analysis
Risk of Bias:
Studies will be categorized based on their risk of bias, as assessed during the quality assessment phase. The analysis will be repeated excluding studies with a high risk of bias to evaluate whether their inclusion significantly affects the overall results. This will help ascertain the reliability of the pooled estimates.

Effect of Study Quality:

Sensitivity analyses will be conducted to determine how the exclusion of lower-quality studies impacts the overall findings. This may involve removing studies scoring below a certain threshold on the Cochrane Risk of Bias Tool.
Different Statistical Models:

The primary meta-analysis will be conducted using both random-effects and fixed-effects models. Sensitivity analysis will compare results obtained from these two models to assess how the choice of statistical approach influences the pooled estimates and the interpretation of heterogeneity.

Country(ies) involved USA and IRAN.

Keywords cutaneous leishmaniasis; treatment outcome; adverse effects; network meta-analysis; randomized controlled trials; systematic review.

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