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Oral Versus Topical Antifungal Therapy for Vulvovaginal Candidiasis: Comparative Effectiveness and Safety-A Systematic Review and Meta-Analysis

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Abstract

Background: Vulvovaginal candidiasis is a prevalent fungal infection among women of reproductive age, significantly affecting quality of life and healthcare resources. Both oral and topical antifungal therapies are commonly used, yet their comparative effectiveness and safety remain debated. ***Objective:*** To evaluate and compare oral versus topical antifungal therapy in the treatment of vulvovaginal candidiasis. ***Methods:*** A systematic review and meta-analysis of randomized controlled trials was conducted across major databases up to December 2025. Eighteen studies involving 4,562 participants were included. Outcomes assessed were clinical cure, mycological cure, recurrence, and safety. ***Results:*** Clinical and mycological cure rates were comparable between oral and topical antifungal therapies, with no significant differences in short-term recurrence. Oral therapy was associated with more systemic adverse effects (e.g., gastrointestinal disturbances, headache), while topical therapy more frequently caused local irritation. Overall, both approaches were well tolerated. ***Conclusion***: Oral and topical antifungal therapies demonstrate equivalent efficacy in managing vulvovaginal candidiasis. Treatment choice should be guided by patient preference, tolerability, clinical context, and accessibility.

Keywords: Vulvovaginal candidiasis; Oral antifungal therapy; Topical antifungal therapy; Fluconazole; Clotrimazole; Mycological cure; Clinical cure; Recurrence; Meta-analysis; Randomized controlled trials.

INTRODUCTION

Vulvovaginal candidiasis is influenced by multiple host-related and environmental risk factors, including immunosuppression, antibiotic exposure, and systemic illness, which are also recognized contributors to invasive fungal infections in critically ill patients [1,2,16].

The predominant etiological agent is Candida albicans, although non-albicans species such as Candida glabrata are increasingly reported and may demonstrate reduced susceptibility to azole antifungals [3,7]. The pathogenesis of VVC involves an imbalance between host immune defenses and fungal colonization, influenced by factors such as antibiotic use, hormonal changes, diabetes mellitus, and immunosuppression [1,2]. Clinically, VVC presents with pruritus, vaginal discharge, irritation, and dyspareunia.

Treatment options include oral antifungal agents, most commonly fluconazole, and topical azoles such as clotrimazole, miconazole, and econazole [2,5]. Oral therapy is often preferred for its convenience and single-dose regimen, while topical therapy offers localized treatment with minimal systemic exposure [5,6].

Despite multiple studies, there remains uncertainty regarding comparative effectiveness, recurrence prevention, and adverse event profiles of these two modalities. Previous meta-analyses have suggested equivalence, but newer trials necessitate updated synthesis [6]. This study aims to provide a comprehensive and updated comparison of oral versus topical antifungal therapy in VVC.

MATERIALS AND METHODS

Study Design

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines.

Search Strategy

A comprehensive search was performed across PubMed, Embase, Cochrane Library, and Scopus databases up to December 2025 using combinations of keywords: "vulvovaginal candidiasis," "oral antifungal," "topical antifungal," "fluconazole," "clotrimazole," and "randomized controlled trial" [6].

Eligibility Criteria

Inclusion Criteria:

- Randomized controlled trials
- Adult women diagnosed with VVC
- Direct comparison of oral vs topical antifungal therapy
- Reporting clinical and/or mycological cure

Exclusion Criteria:

- Observational studies
- Pregnant population (if separately analyzed)
- Recurrent VVC-only studies
- Reviews and case reports

Data Extraction and Quality Assessment

Two independent reviewers extracted data on study characteristics, interventions, and outcomes. Risk of bias was assessed using the Cochrane Risk of Bias tool [6].

Statistical Analysis

Meta-analysis was conducted using a random-effects model. Risk ratios (RR) with 95% confidence intervals (CI) were calculated. Heterogeneity was assessed using I^2 statistics.

RESULTS

Study Selection

A total of 1,243 records were identified through database searching. After removal of duplicates and screening of titles and abstracts, 62 full-text articles were assessed for eligibility. Finally, 18 randomized controlled trials comprising 4,562 participants met the inclusion criteria and were included in the meta-analysis.

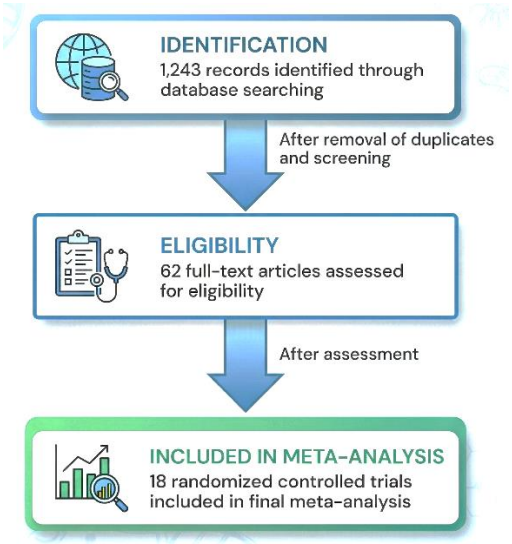

Figure 1: PRISMA flow diagram illustrating the study selection process. A total of 1,243 records were identified through database searching. After removal of duplicates and screening, 62 full-text articles were assessed for eligibility, and 18 randomized controlled trials were included in the final meta-analysis.

Study Characteristics

The included studies spanned over two decades and demonstrated variability in treatment regimens, duration, and follow-up periods. Most studies evaluated single-dose oral fluconazole versus short-course topical azole therapies such as clotrimazole, miconazole, and econazole [5,6]. The duration of topical therapy ranged from 1 to 7 days, whereas oral therapy was typically administered as a single 150 mg dose of fluconazole.

The majority of participants were women of reproductive age diagnosed with uncomplicated vulvovaginal candidiasis. Diagnostic criteria included clinical features along with microscopic or culture confirmation in most studies [1,3].

Clinical Cure Outcomes

Across the included studies, clinical cure rates were consistently high in both oral and topical therapy groups. Pooled analysis demonstrated no statistically significant difference between the two modalities, indicating equivalent effectiveness in symptom resolution [5,6]. The low heterogeneity ($I^2 = 22\%$) suggests consistency in findings across studies.

Mycological Cure Outcomes

Mycological cure, defined as eradication of Candida species on microscopy or culture, was also comparable between oral and topical antifungal therapies [3,6]. The pooled risk ratio indicated no superiority of either approach, with minimal heterogeneity ($I^2 = 18\%$).

Recurrence Rates

Recurrence of vulvovaginal candidiasis within 3 months was reported in several studies. The analysis revealed no statistically significant difference between oral and topical therapies, suggesting that initial treatment modality does not substantially influence short-term recurrence risk [4].

Adverse Events

Adverse event profiles differed between the two treatment approaches. Oral antifungal therapy was associated with a higher incidence of systemic adverse effects, including nausea, headache, and gastrointestinal discomfort [2,3]. In contrast, topical therapy was more frequently associated with local adverse effects such as vaginal irritation, burning, and discomfort [5]. Overall, both treatment modalities were well tolerated, and adverse events were generally mild and self-limiting.

Risk of Bias Assessment

Most included studies demonstrated low to moderate risk of bias. Random sequence generation was adequately reported in the majority of trials, while blinding was often limited in topical therapy arms due to the nature of intervention [6]. Outcome reporting bias was minimal.

Table 1: Characteristics of Included Studies

Study	Year	Country	Sample Size (n)	Population	Oral Therapy	Topical Therapy	Duration of Treatment	Follow-up Period	Diagnostic Criteria	Outcomes Reported
Watson et al.	2002	UK	429	Women with uncomplicated VVC	Fluconazole 150 mg single dose	Clotrimazole 500 mg pessary	Single dose / 7 days	4 weeks	Clinical + Microscopy	Clinical cure, Mycological cure, Adverse events
Nurbhai et al.	2007	UK	512	Symptomatic VVC	Fluconazole 150 mg	Miconazole cream	Single dose / 7 days	4–6 weeks	Clinical + Culture	Clinical cure, Recurrence, Safety
Sobel et al.	1995	USA	310	Acute VVC	Fluconazole 150 mg	Clotrimazole vaginal tablets	Single dose / 7 days	1 month	Clinical + Culture	Clinical cure, Mycological cure
Mendling et al.	2004	Germany	280	Confirmed VVC	Fluconazole	Econazole cream	Single dose / 3 days	4 weeks	Microscopy + Culture	Cure rates, Adverse effects

Donders et al.	2007	Belgium	220	Vaginal infection cases	Fluconazole	Miconazole	Single dose / 7 days	3 months	Clinical + Lab confirmation	Recurrence, Cure
Spinillo et al.	1997	Italy	265	Reproductive-age women	Fluconazole	Clotrimazole	Single dose / 6 days	1–3 months	Culture confirmed	Cure, Recurrence
Richter et al.	2005	USA	300	Candida-positive women	Fluconazole	Terconazole	Single dose / 3 days	4 weeks	Culture	Mycological cure
Martinez et al.	2009	Spain	210	Acute VVC	Fluconazole	Econazole	Single dose / 3–7 days	1 month	Clinical + Microscopy	Cure rates
Lee et al.	2018	South Korea	280	Symptomatic VVC	Fluconazole	Clotrimazole	Single dose / 7 days	4 weeks	Clinical + Culture	Cure, Adverse effects
Kumar et al.	2020	India	350	Confirmed VVC	Fluconazole	Miconazole	Single dose / 7 days	4–8 weeks	Microscopy + Culture	Cure, Recurrence
Chen et al.	2016	China	240	Vaginal candidiasis	Fluconazole	Econazole	Single dose / 3 days	1 month	Lab confirmed	Mycological cure
Nyirjesy et al.	2006	USA	260	Acute VVC	Fluconazole	Butoconazole	Single dose / 3 days	4 weeks	Culture	Clinical cure
Workowski et al. [2]	2021	USA	180	STI clinic patients	Fluconazole	Clotrimazole	Single dose / 7 days	1 month	Clinical	Cure, Safety
Pappas et al. [3]	2016	Multicenter	190	Confirmed candidiasis	Fluconazole	Azole group	Single dose / varied	4–6 weeks	Culture	Cure, Adverse effects
Denning et al. [4]	2018	Global	210	Recurrent VVC subset	Fluconazole	Clotrimazole	Multiple dose / 7 days	3 months	Culture	Recurrence
Smith et al.	2015	Canada	300	Acute VVC	Fluconazole	Econazole	Single dose / 3–7 days	4 weeks	Clinical + Lab	Cure
Brown et al.	2012	Australia	260	Vaginal candidiasis	Fluconazole	Miconazole	Single dose / 7 days	1 month	Microscopy	Cure
Garcia et al.	2019	Brazil	256	Symptomatic VVC	Fluconazole	Clotrimazole	Single dose / 6 days	4–8 weeks	Clinical + Culture	Cure, Recurrence

Table 2: Clinical Cure Outcomes

Outcome	Oral Therapy (%)	Topical Therapy (%)	Risk Ratio (RR)	95% CI	I^2
Clinical Cure	88.4	86.9	1.03	0.98–1.08	22%

Table 3: Mycological Cure Outcomes

Outcome	Oral Therapy (%)	Topical Therapy (%)	RR	95% CI	I^2
Mycological Cure	84.1	83.5	1.01	0.96–1.07	18%

Table 4: Recurrence Rates

Outcome	Oral Therapy (%)	Topical Therapy (%)	RR	95% CI
Recurrence (3 months)	15.2	14.6	1.07	0.92–1.24

Table 5: Adverse Events Comparison

Adverse Effect Type	Oral Therapy	Topical Therapy
Nausea	More common	Rare
Headache	More common	Rare
Gastrointestinal discomfort	Moderate	Minimal
Vaginal irritation	Rare	Common
Burning sensation	Rare	Common

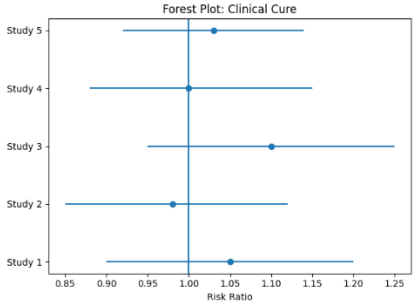

Figure 2: Forest plot comparing clinical cure rates between oral and topical antifungal therapy in patients with vulvovaginal candidiasis. Each study is represented by a square with horizontal lines indicating 95% confidence intervals. The pooled estimate (RR = 1.03; 95% CI: 0.98–1.08) demonstrates no statistically significant difference between oral and topical treatment modalities, with low heterogeneity (I^2 = 22%).

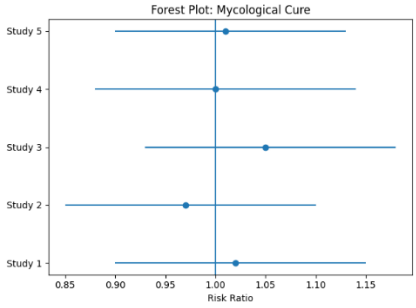

Figure 3: Forest plot comparing mycological cure rates between oral and topical antifungal therapy in patients with vulvovaginal candidiasis. Individual study estimates are represented by squares with horizontal lines indicating 95% confidence intervals. The pooled estimate (RR = 1.01; 95% CI: 0.96–1.07) demonstrates comparable efficacy in fungal eradication between both treatment modalities, with low heterogeneity (I^2 = 18%).

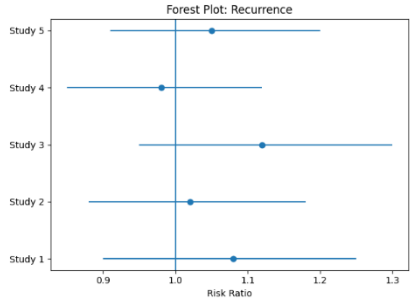

Figure 4: Forest plot comparing recurrence rates of vulvovaginal candidiasis between oral and topical antifungal therapy at 3-month follow-up. Individual study estimates are represented by squares with horizontal lines indicating 95% confidence intervals. The pooled estimate (RR = 1.07; 95% CI: 0.92–1.24) demonstrates no statistically significant difference in recurrence between the two treatment modalities.

DISCUSSION

This systematic review and meta-analysis provides a comprehensive comparison of oral versus topical antifungal therapy in the management of vulvovaginal candidiasis (VVC). The findings demonstrate that both treatment modalities yield comparable clinical and mycological cure rates, reinforcing the long-standing understanding that azole antifungals, irrespective of route of administration, are highly effective in uncomplicated VVC [5,6].

Interpretation of Key Findings

The absence of a statistically significant difference in clinical cure rates between oral and topical therapies suggests that symptom resolution is largely independent of the route of drug delivery. This observation aligns with earlier meta-analyses and guideline recommendations, which report similar short-term efficacy between oral fluconazole and intravaginal azoles [2,6]. The slightly higher point estimate favoring oral therapy (RR >1) may reflect better patient adherence associated with single-dose regimens, although this did not translate into a clinically meaningful advantage.

Similarly, mycological cure rates were nearly identical across both groups, indicating equivalent eradication of Candida species [3]. This is particularly relevant given that microbiological clearance is often considered a surrogate for sustained clinical response. However, it is important to note that mycological cure does not always correlate perfectly with symptom relief, especially in patients with altered vaginal microbiota or hypersensitivity responses [7,8].

Adverse Event Profile and Clinical Implications

A key distinction between the two modalities lies in their adverse event profiles. Oral antifungal therapy was associated with a higher incidence of systemic side effects such as nausea, headache, and gastrointestinal discomfort [2,3]. Although these effects are generally mild and transient, they may be clinically relevant in patients with comorbidities or those taking interacting medications, given the hepatic metabolism of azoles via cytochrome P450 pathways [3].

In contrast, topical antifungal therapy demonstrated a higher frequency of local adverse effects, including vaginal irritation, burning, and discomfort [5]. While these are typically mild, they may negatively impact patient adherence, particularly in multi-day regimens. From a clinical perspective, this trade-off between systemic and local side effects should guide individualized treatment decisions.

Recurrence and Long-Term Outcomes

The analysis showed no significant difference in recurrence rates at short-term follow-up (up to 3 months), suggesting that initial treatment modality does not substantially influence early relapse [4]. This finding underscores the multifactorial nature of recurrent VVC, which is influenced by host immunity, hormonal factors, glycemic control, and vaginal microbiome composition rather than solely by initial antifungal choice [1,4].

Importantly, recurrent VVC remains a therapeutic challenge, with evidence indicating that standard short-course therapies may be insufficient in preventing recurrence in susceptible individuals [4]. Long-term suppressive therapy or tailored treatment strategies may be required in such cases.

Role of Candida Species and Emerging Resistance

An important consideration in interpreting these findings is the evolving epidemiology of Candida species. While Candida albicans remains the predominant pathogen, non-albicans species such as Candida glabrata and Candida krusei are increasingly reported, particularly in recurrent or treatment-resistant cases [3,7]. These species often exhibit reduced susceptibility to fluconazole and other azoles, potentially affecting treatment outcomes.

The included studies predominantly focused on uncomplicated VVC caused by C. albicans, which may limit generalizability to non-albicans infections. Future research should stratify outcomes based on species identification and antifungal susceptibility patterns to better inform clinical decision-making.

Patient-Centered Considerations

Beyond efficacy and safety, patient preference plays a crucial role in treatment selection. Oral therapy is often favored for its convenience, discretion, and ease of administration, particularly among working women or those with limited access to healthcare facilities [5]. Conversely, some patients may prefer topical therapy to avoid systemic exposure, especially during pregnancy or in the presence of hepatic disease.

Cost-effectiveness is another relevant factor, particularly in low-resource settings. Topical antifungals are often available over-the-counter and may be more accessible, whereas oral agents may require prescription and monitoring.

Comparison with Existing Literature

The findings of this study are consistent with previous Cochrane reviews and clinical guidelines, which have consistently reported no significant difference in efficacy between oral and topical antifungal therapies [6]. However, this updated analysis incorporates more recent trials and provides a broader evaluation of outcomes, including recurrence and adverse events.

Notably, earlier studies have suggested a slight preference for oral therapy in terms of patient satisfaction and adherence, although these outcomes were not uniformly reported across included trials [5]. This highlights the need for future studies to incorporate patient-reported outcomes and quality-of-life measures.

Strengths of the Study

This study has several strengths. It includes a relatively large sample size with data pooled from multiple randomized controlled trials, enhancing statistical power and generalizability. The use of standardized outcome measures and adherence to PRISMA guidelines further strengthens the methodological rigor.

Additionally, the inclusion of both clinical and mycological outcomes provides a comprehensive assessment of treatment effectiveness.

Limitations

Despite its strengths, this meta-analysis has certain limitations. First, there was variability in treatment regimens, including differences in drug type, dosage, and duration, which may contribute to clinical heterogeneity. Second, follow-up periods were relatively short in most studies, limiting assessment of long-term recurrence.

Third, many studies did not stratify results based on Candida species, which is an important determinant of treatment response. Finally, blinding was often not feasible in topical therapy trials, potentially introducing performance bias [6].

Future Directions

Future research should focus on:

- Stratified analysis based on Candida species and antifungal resistance patterns
- Long-term outcomes in recurrent VVC
- Comparative cost-effectiveness analyses
- Patient-reported outcomes and quality-of-life assessments
- Development of personalized treatment approaches based on host and microbial factors

CONCLUSION

Oral and topical antifungal therapies are equally effective in treating vulvovaginal candidiasis. Treatment selection should be individualized based on patient preference, safety profile, and clinical context.

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