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A meta-analysis on anti-fungal drug efficacy in patients with oropharyngeal candidiasis in immunocompromised patients

Osamah Soliman Al Alawi[1], Ahmed Shaker Ali[2], Duaa Bakhshwin[3], Fahad Hameed Aljahdali[4]

[1]Medical supply administration, Jeddah, Saudi Arabia, Pharmacology Department, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia, Email: oasamah1402@gmail.com
[2]Faculty of Medicine, Dept of Clinical Pharmacology, King Abdulaziz University, KSA, Email: asali@kau.edu.sa;
[3]Faculty of Medicine, Dept of Clinical Pharmacology, King Abdulaziz University, KSA, Email: dbakhshwin@kau.edu.sa
[4]Senior Pharmacist, Compliance management in Jeddah, Email: Fahadaljahdali@hotmail.com

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ABSTRACT

Background: Oropharyngeal candidiasis (OPC) is fungal infection caused by Candida albicans.

Aim: To compare the efficiency of different antifungal drugs in the management of oropharyngeal candidiasis in immunocompromised cases.

Patients & methods: Fifteen investigation have been involved in this systematic review and meta-analysis, with 3646 immunocompromised patients with soph pharynx geal or oropharyngeal candidiasis. In all studies, cases have been assigned to receive Fluconazole, Nystatin, Anidulafungin, Itraconazole, or a placebo. Two authors independently searched online databases including EMBASE, Scopus MEDLINE, Cochrane Library, PubMed, and Web of Science

Results: Regarding the assessment of Microbiological Success for different antifungal drugs, fluconazole showed RR with 95% CI: 0.53 [0.35,0.7], A random effect model was applied, and heterogeneity was detected among our pooled studies with chi-p<0.001 and I2 =97%. The rate of adverse events for fluconazole were (22.8%) lower than that for itraconazole (64.5%) and micafungin (54.8%), and most adverse events were mild elevation of transaminase levels, gastrointestinal symptoms, and oral burning sensation. Our pooled studies for this outcome were heterogeneous; therefore, a random-effects model was applied with a chi-p=0.001 and I2=100%. Our pooled studies for mortality rate reported RR with 95%CI ,0.09 [0.05, 0.13] and, 0.1 [-0.016, 0.232] for fluconazole and itraconazole, respectively.

Conclusion: Fluconazole is recommended as an antifungal agent for oropharyngeal candidiasis in immunosuppressed cases, as it was effective in producing a successful clinical outcome and had reasonable safety compared to antifungal agents.

Keywords: Oropharyngeal candidiasis, Antifungal drugs, Immunocompromised.

INTRODUCTION

Oropharyngeal candidiasis (O, predominantly caused by *Candida albicans*, is the most common oral fungal infection. It frequently occurs in individuals with weakened immune systems or those undergoing treatments that disrupt the normal microbial balance in the oral cavity. Common risk factors include the utilization of antibiotics, glucocorticoids, immunosuppressants, and the presence of conditions such as diabetes, organ transplantation, and HIV infection. Additionally, denture wearers and individuals receiving cancer treatments, including radiation and chemotherapy, are particularly susceptible to OPC**(1-4)**.

Gap in Knowledge: Despite the availability of multiple antifungal agents, there remains a lack of comprehensive data directly comparing all available treatments for OPC. Most RCTs have been limited to comparisons between two agents, leaving gaps in our understanding of the relative effectiveness and safety of various antifungals, particularly in immunocompromised populations, such as those with HIV or cancer. Moreover, the evidence regarding the long-term outcomes, including recurrence rates and adverse effects, is still insufficient to guide clinical decision**(5-7)**. The variability in study designs and patient populations further complicates drawing clear conclusions on the most effective treatment strategy for OPC in immunocompromised patients.

Research Question: This systematic review and meta-analysis aim to fill this gap by comparing the efficacy and safety of various antifungal medications in the management of OPC, with a focus on fluconazole. Specifically, it will address the question: "What is the most efficient and safe antifungal treatment for oropharyngeal candidiasis in immunocompromised patients, particularly those with HIV or cancer?" The findings will provide clinicians with evidence-based insights to guide optimal treatment selection in resource-limited settings or when access to antifungal medications is restricted.

Patients & Methods

Search strategy: Two authors independently investigated the online databases involving EMBASE, Scopus MEDLINE, Cochrane Library, PubMed & Web of Science databases by combing Mesh and text keywords of "antifungal drugs," "oropharyngeal candidiasis," "immunocompromised,"", "Fluconazole,"", "Nystatin,"", "Antifungal,"", "Itraconazole,"", "Amphotericin B."". Electronic searches included studies published in various languages to minimize publication bias.

Inclusion criteria: We included clinical trials and observational studies comparing antifungal drugs for oropharyngeal candidiasis in immunocompromised patients, both randomized controlled trials (RCTs) and observational investigation were included to provide a comprehensive analysis and studies reporting outcomes, such as clinical response rates, adverse effects, and any relevant laboratory data.

Data Extraction: The following data have been extracted:author name, year of publication, research design, sample size, age, sex, interventions, dosage, duration of treatment, outcomes, and adverse events.

RESULTS

Literature search results

The PRISMA flow diagram (Figure 1) outlines the research selection process. A total of 630 records have been initially retrieved through the literature search. Following removing 101 duplicates using endnote, the titles and abstracts of the remaining records have been screened. Eighteen articles were deemed eligible for full-text review, and 15 have been ultimately involved in the meta-analysis**(8-22).**Additionally, references from the selected studies were manually searched, but no further articles were identified for inclusion.

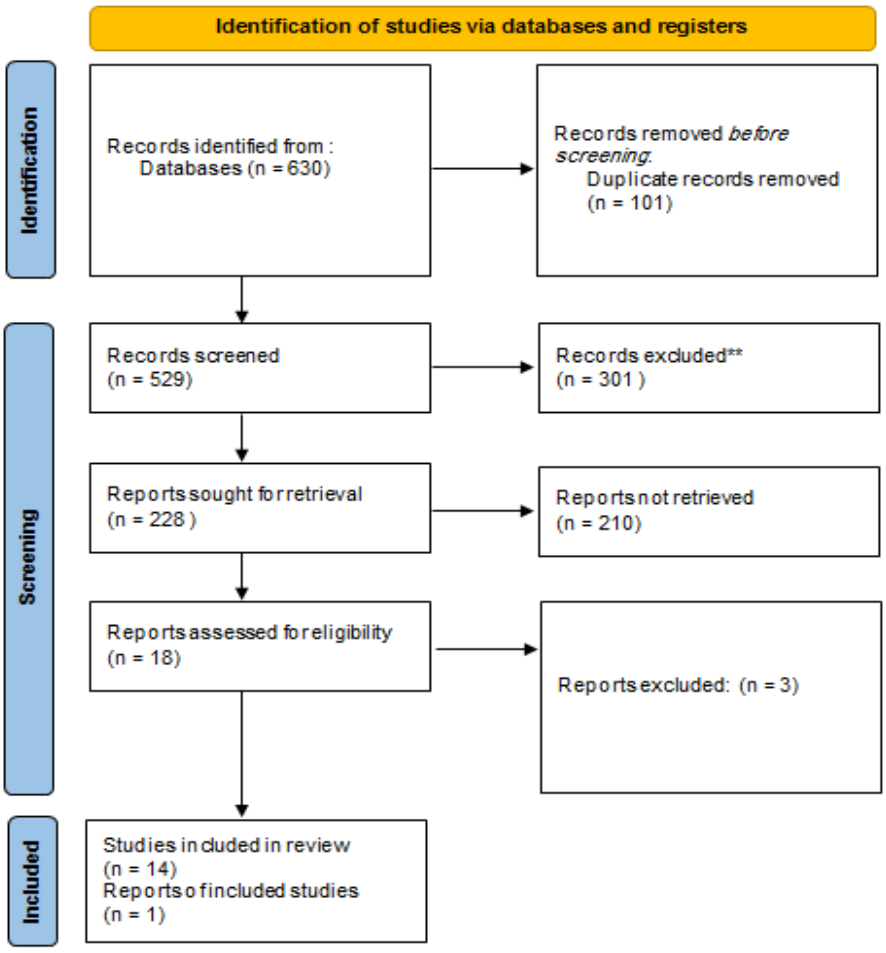

Figure 1: The PRISMA flow diagram

Characteristics of Included Studies

This systematic review and meta-analysis consisted of fifteen investigations, including a total of 3,646 immunocompromised cases with esophageal or oropharyngeal candidiasis. cases were randomly randomized to receive either fluconazole, nystatin, antifungal medications, itraconazole, or a placebo; this was the case across all of the investigations. A summary of the key characteristics of these investigations is provided in **Table 1.**

Table 1: baseline characteristics of the included population

Study ID	Study design	Intervention	sample size	age	gender	dosage	duration of treatment
Goins (23)	prospective RCT (pilot study)	Fluconazole oral	19	1 to 12 months	NR	3 mg /kg daily	7 days
		Nystatin oral suspension	28			4 times /day	10 days
Krause (17)	RCT	Fluconazole oral	301	18-65	145M/156F	200 mg on day	14-21 days
		Anidulafungin IV	300	18-69	127M/173F	1, followed by 100 mg per day	
Lashof (18)	multicenter comparative study	Fluconazole oral	126	54	67F/53M	100 mg / day	10 days
		Itraconazole capsule	126	55	55F/44M	200 mg / day	15 days
Linpiyawan (8)	prospective clinical trial	clotrimazole torch	15	32 years	20M/9F	10 mg/ 5 times /day	2 weeks
		itraconazole oral solution	14			100 mg/10 ml /twice daily	
Nairy (21)	clinical trial	Fluconazole oral	15	32 (3.5)	10M/5F	100mg/day	14 days
		Fluconazole gel	15			5 ml/12 hour	
Pagani (14)	RCT	fluconazoe oral	114	38(8)	NR	200mg /day	7 days
		PLACEBO	29	35(7)		NR	7 days
Schürmann (24)	RCT	fluconazole	191	18-75 years	NR	400 mg on day1 then 200 mg daily	15 days
		voriconazoe	200			200 mg B.I.d	14 days
Smith (11)	RCT	itraconazole oral	187	37.8(8.5)	178M/9F	100mg	104 weeks
		PLACEBO	187	37.6(8.4)	172M/15F	NR	
Taillandier (9)	RCT	fluconazole oral suspension	150	84(8)	36M/114F	10mg/ml/day	14 days
		Amphotericin B	155	84(8)	49M/106F	0.5g/5ml/3 times daily	
Vazquez (20)	RCT	fluconazole	172	36.4(7.8)	131M/47F	200mg in day 1 then 100mg for13 days	14 days
		posaconazole	178	37.6(9.1)	131M/41F		
Vazquez (20)	prospective single center study	Alcohol-Based melaleuca	12	25-51 years	25M	4 times /day	2-4 weeks
		Alcohol-free melaleuca	13				
Viljoen (22)	RCT	Fluconazole	38	18-65 years	33M/5F	200 mg day 1 then 100 mg	14 days
		Isavuconazole	121		99M/22F	200/50mg QD/400 mg weekly/400/100mg QD	
Villanueva (15)	RCT	fluconazole	94	36(12)		200 mg	7-21 days
		caspofungin	83	37(11)		50 mg	
Wet (16)	RCT	fluconazole IV	60	35.5(8.1)	46.7% Male	200 mg /day	14-21 days
		micafungin IV	185	36.7(8)	48.2% M	50, 100, or 150 mg /day	

Risk of Bias Assessment

The 15 randomized controlled trials (RCTs) involved in this meta-analysis exhibited a range of low to high possibility of bias, as evaluated using the Cochrane Risk of Bias (ROB) Tool 1. The risk of bias graph and summary are shown in Figure 2.

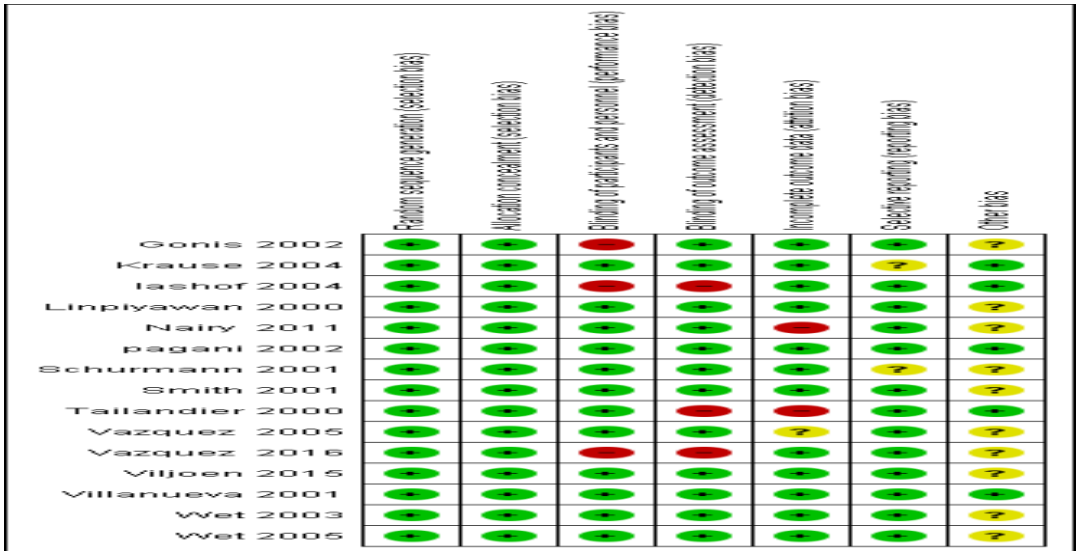

Figure 2: Risk of Bias Assessment

Outcomes

Efficacy Outcomes

Clinical Success

Our pooled Relative Risk (RR) analysis demonstrated that fluconazole, regardless of the route of administration, achieved significantly higher clinical success compared to the following antifungal agents: Voriconazole, Nystatin, Itraconazole, Clotrimazole, Amphotericin, Caspofungin, melaleuca, and placebo, with a pooled RR of 0.86 (ninety-five percent CI: 0.80–0.90). High heterogeneity was detected among the included studies, with a chi-squared p-value of <0.001 and an I^2 of 94% (Figure 3)

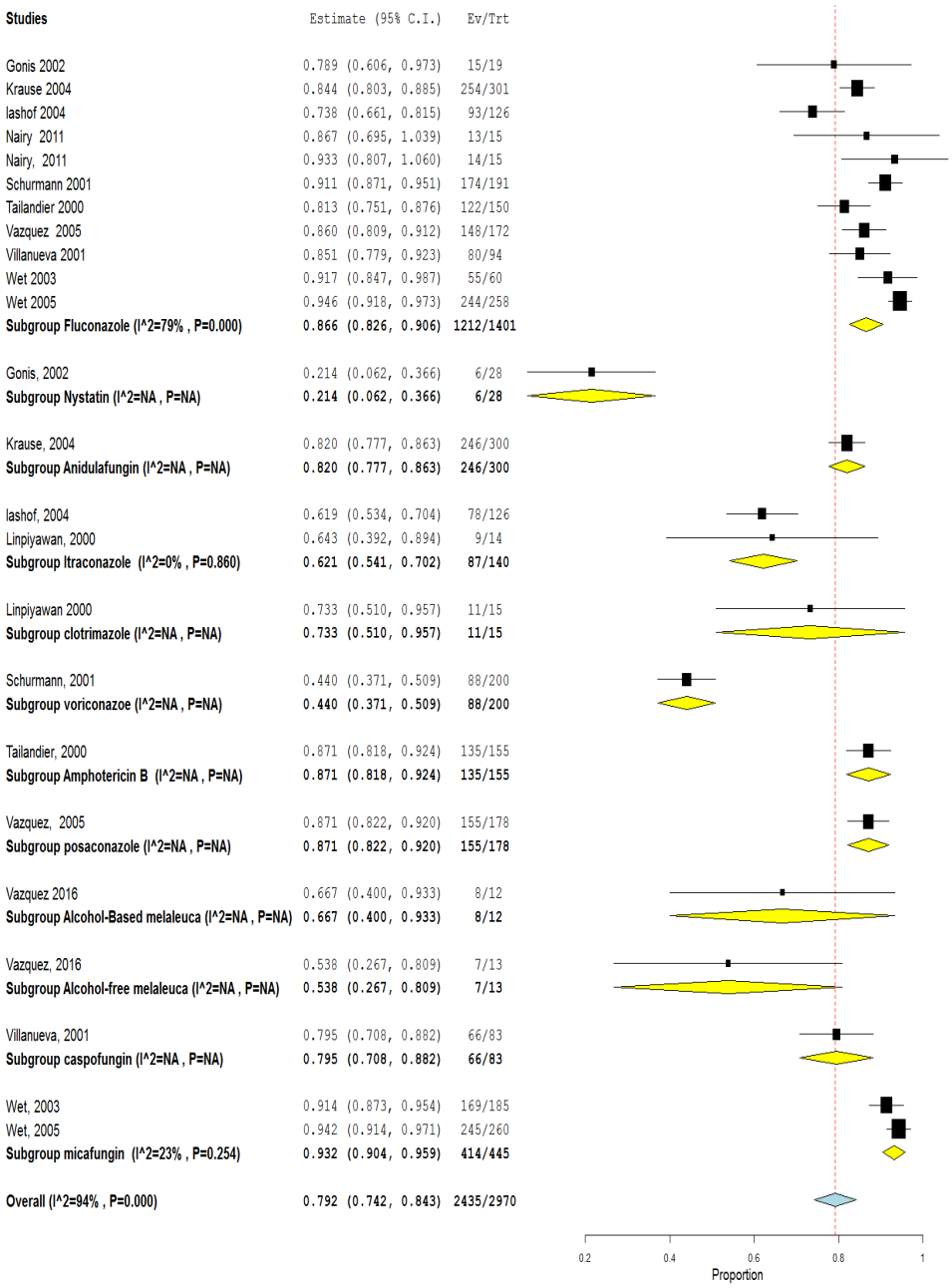

Figure 3

Microbiological Success

In assessing microbiological success across different antifungal treatments, fluconazole demonstrated a pooled Relative Risk (RR) of 0.53 (ninety-five percent CI: 0.35–0.70). A random-effects model was applied, revealing significant heterogeneity among the pooled investigations (chi-p < 0.001, I^2 = 97%) (Figure 4).

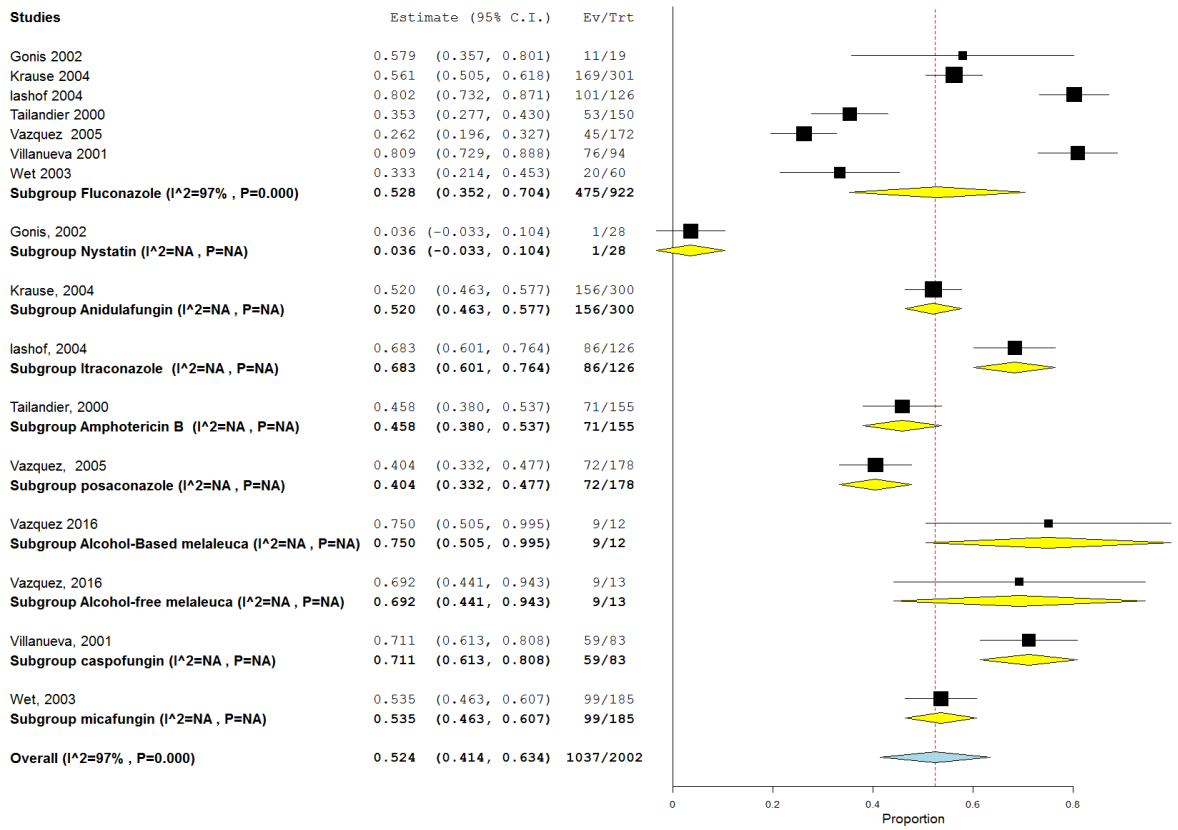

Figure 4

Clinical Relapse

For clinical relapse, the pooled RR was 0.30 (ninety-five percent CI: 0.13–0.48) for fluconazole and 0.26 (ninety-five percent CI: 0.16–0.36) for itraconazole. Significant heterogeneity was present in the investigations (chi-p < 0.00001, I^2 = 96%) (Figure 5).

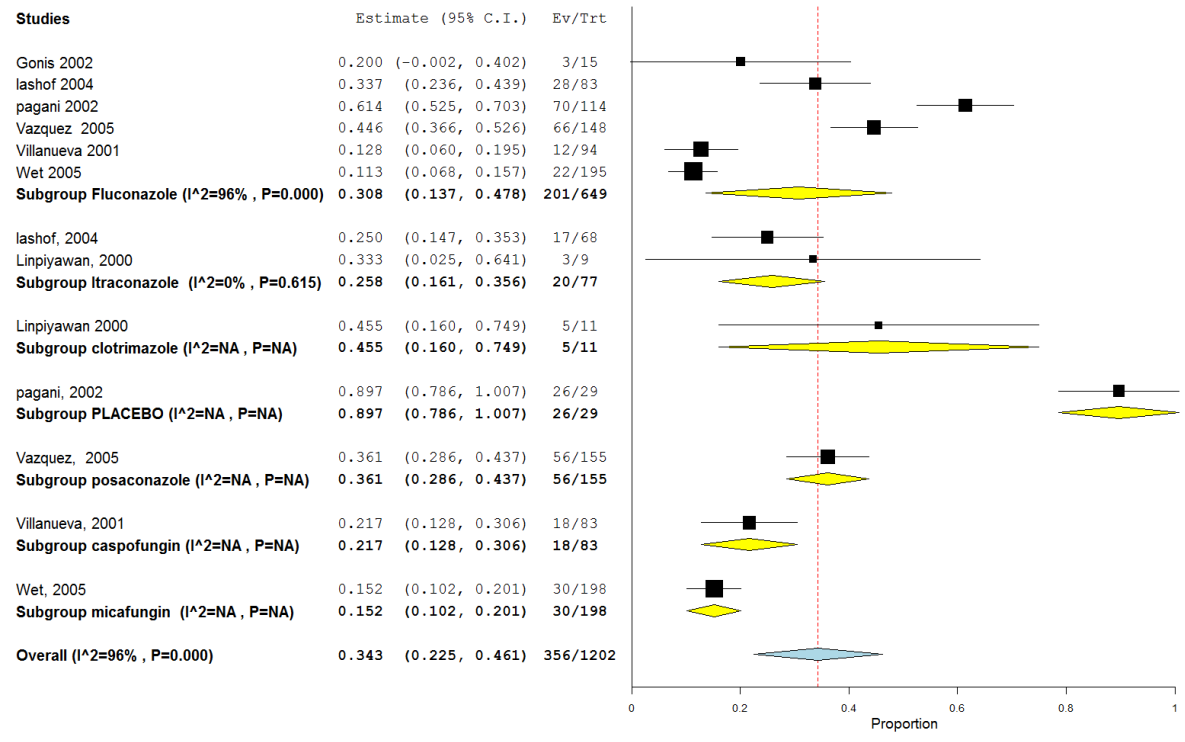

Figure 5

Microbiological Relapse

Regarding microbiological relapse, fluconazole had a pooled RR of 0.30 (ninety-five percent CI: 0.24–0.42) and itraconazole 0.29 (ninety-five percent CI: 0.19–0.39). Homogeneity was observed among the studies (chi-p = 0.6, I^2 = 0%) (Figure 6).

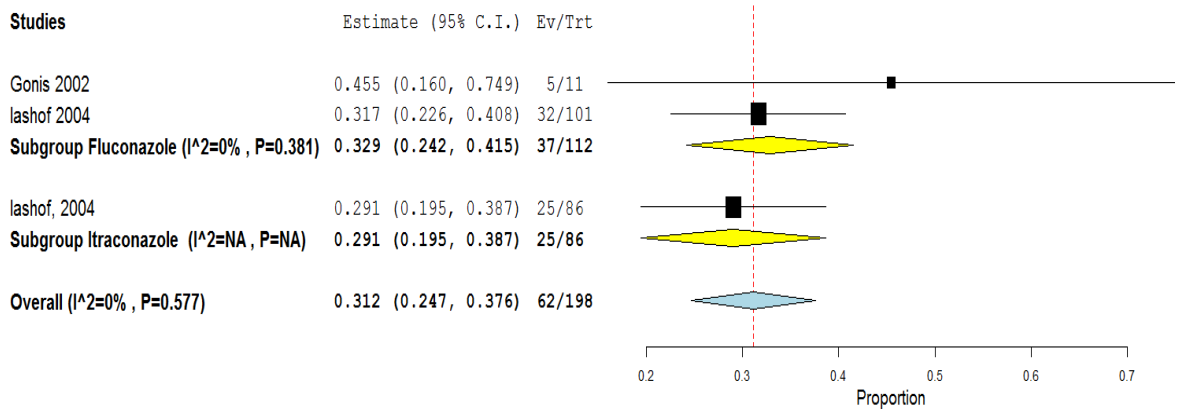

Figure 6

Safety Outcomes

Adverse Events

The incidence of adverse events was lower for fluconazole (22.8%) compared to itraconazole (64.5%) and micafungin (54.8%). Most adverse events included mild transaminase elevation, gastrointestinal symptoms, and oral burning sensations. Due to the significant heterogeneity among investigations (chi-p = 0.001, I^2 = 100%), a random-effects model has been applied (Figure 7).

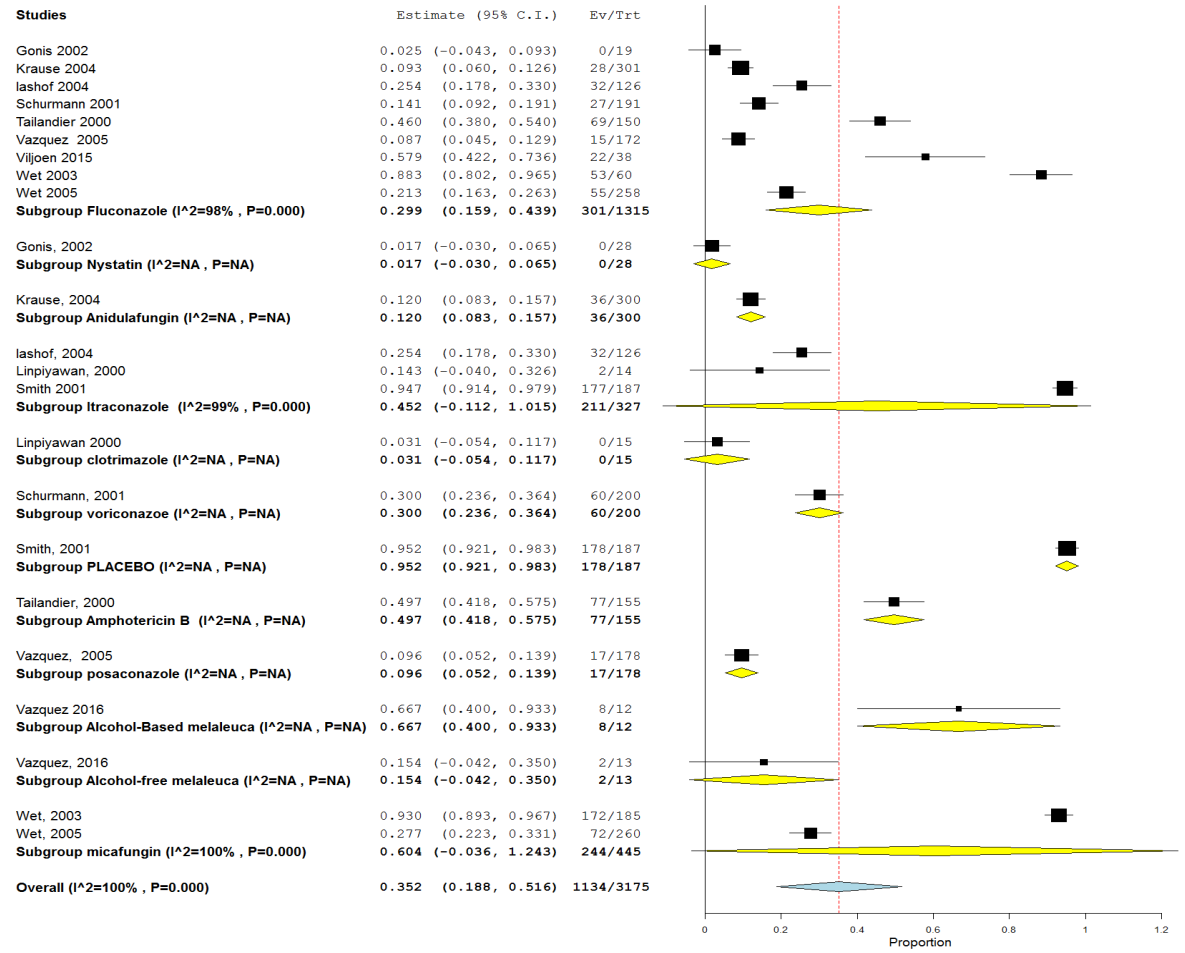

Figure 7

Mortality

Pooled mortality rates showed an RR of 0.09 (95% CI: 0.05–0.13) for fluconazole and 0.10 (95% CI: -0.016–0.232) for itraconazole. Most mortalities were attributed to immunosuppression rather than drug-related causes. Moderate heterogeneity was found (chi-p = 0.03, I^2 = 67%) (Figure 8).

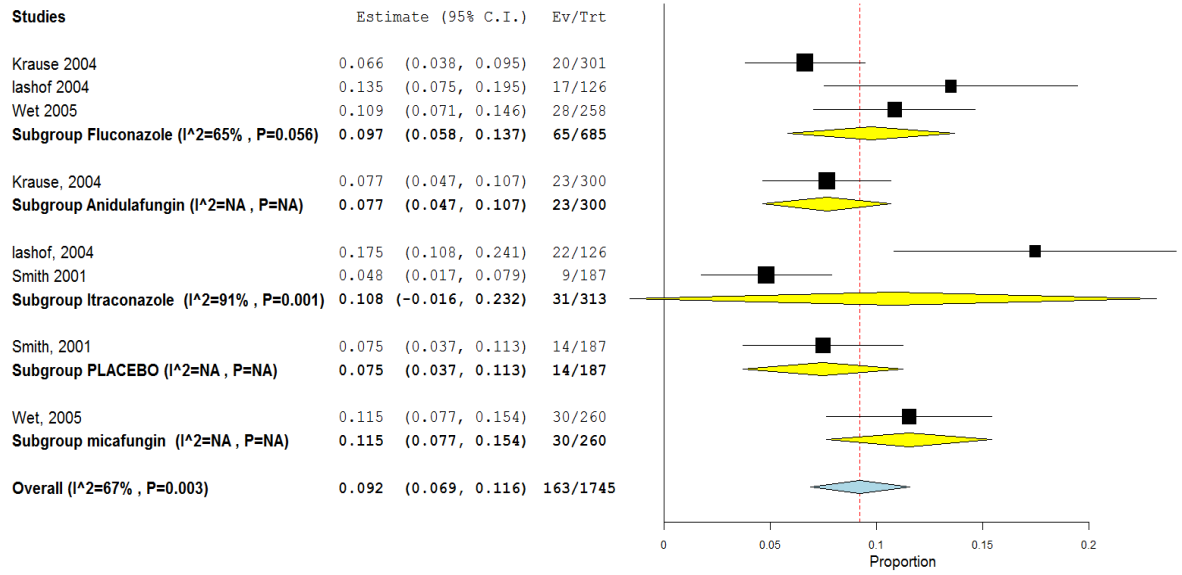

Figure 8

DISCUSSION

Oropharyngeal candidiasis (OPC) occurs when there is an excessive proliferation of normal fungal, Candida spp., in the throat and mouth. OPC is frequently observed in individuals with compromised immune systems, such as those with diabetes, human immunodeficiency virus, or those undergoing chemotherapy(Vila, Sultan et al. 2020)**(25).**

According to the current guidelines from the Infectious Disease Society of America, topical antifungals like nystatin and clotrimazole troches could be used to treat early episodes of oropharyngeal candidiasis. However, individuals with HIV are at a higher risk for recurrence. Additionally, most of topical formulations can be burdensome to administer, necessitating frequent applications and generally offering lower efficacy compared to systemic therapies.(Rajadurai, Maharajan et al. 2021)**(5).**

Oral fluconazole or itraconazole is often effective for managing OPC through systemic therapy. However, fluconazole-resistant Candida species have been documented extensively. The prevalence of oropharyngeal or esophageal candidiasis caused by these resistant strains is estimated to be around 5%. Recently, newer antifungal agents likecaspofungin, micafungin and voriconazole have demonstrating promising efficacy in treating mucocutaneous candidiasis**(26)**.

Hence, we carried out this meta-analysis to compare the efficiency of various antifungal medications for the managementof oropharyngeal candidiasis in immunocompromised cases. Fifteen studies were conducted on immunocompromised cases with Esophageal or Oropharyngeal candidiasis treated with antifungal agents including Fluconazole, Nystatin, Antifungal, Itraconazole, Amphotericin B, Voriconazole, Capsofungin, Melaleuca, and Clotrimazole.

Our pooled Relative Risk (RR)showed that fluconazole, regardless of the route of administration, reported significant clinical success compared with the following anti-fungal drugs: Voriconazole, Nystatin, Antifungal, Itraconazole, Clotrimazole, Amphotericin, Capsofungin, melaleuca, and placebo, with RRs and 95% CI: 0.86 [0.8,0.9]. Regarding the assessment of microbiological success of different antifungal drugs, this meta-analysis reported that fluconazole showed significant microbiological success (RR with 95% CI: 0.53 [0.35,0.7]).

Our results align with those of a prior network meta-analysis by **Fang et al. (27)**, which estimated the effectiveness of antifungal agents in treating oral candidiasis.(Fang, Huang et al. 2021) The antifungal drugs utilized in their research were miconazole, fluconazole, itraconazole, amphotericin B, nystatin, ketoconazole, and clotrimazole. Their findings indicate that fluconazole is the most efficient treatment for oral candidiasis. Furthermore, fluconazole showed superior efficacy in lowering the probability of the rate of mycological cure in oral candidiasis compared to other medications.

In their study, **Lashof et al. (18)** systematically evaluated the effectiveness and safety profiles of fluconazole and itraconazole as treatments for patients with cancer and oropharyngeal candidiasis (OPC). The findings revealed that fluconazole not only had a higher rate of clinical success but also demonstrated superior

mycological cure rates compared to itraconazole, highlighting its effectiveness as a preferred treatment option in this patient population.

A prospective investigation performed by **Pagani et al. (14)** assessed the clinical significance of fluconazole resistance in C. albicans and examined the long-term effectiveness and acceptability of fluconazole in preventing Oropharyngeal candidiasis in HIV-positive cases. Their findings revealed that patients receiving weekly fluconazole as secondary prophylaxis experienced fewer relapses of OPC. Additionally, cases of clinically or microbiologically resistant candidiasis were rarely reported in both the treatment and placebo groups, with no significant differences observed between them. The study successfully demonstrated the effectiveness of fluconazole in preventing OPC and confirmed its excellent tolerability over an extendedduration**Lashof, De Bock et al.(18)**.

4o mini

Rajadurai et al. (7) conducted a systematic review and network meta-analysis to evaluate the effectiveness and safety of various antifungal medications for preventing oropharyngeal candidiasis (OPC) in individuals with HIV. Their analysis indicated that fluconazole exhibited the highest effectiveness (SUCRA, 95.6%) and safety (SUCRA, 39.3%) among the antifungal medications assessed for HIV-infected patients. However, as with other antimicrobial agents, it is crucial to consider the potential possibility of resistance alongside the benefits of fluconazole.

Taillandier et al. (9) evaluated the effectiveness and safety of fluconazole oral suspension compared to amphotericin B oral suspension in treating individuals with oropharyngeal candidiasis. According to their findings, fluconazole oral suspension is an effective alternative to amphotericin B oral suspension for the management of individuals with oropharyngeal candidiasis. Negative events were less common in the fluconazole group (46%) than in the amphotericin B group (50%), but the variance was statistically insignificant.

The present metanalysis revealed that the rate of adverse events for fluconazole was (22.8%) lower than that for itraconazole (64.5%) and micafungin (54.8%), and most adverse events were mild elevation of transaminase levels, gastrointestinal symptoms, and an oral burning sensation.

Similarly, our findings were consistent with those of the network meta-analysis conducted by **Rajadurai et al. (7)** who demonstrated that fluconazole has been linked to a 53 % greater likelihood of experiencing negative effects than a placebo (RR, 1.53 (CI interval: 1.02–2.29). Although itraconazole is considered safer than alternative treatments, the observed difference in safety was statistically insignificant (RR 0.78, ninety-five percent CI: 0.40–1.51). Itraconazole was associated with a 96 % greaterprobability of experiencing side effects than placebo.

Similarly, this study was consistent with **Sholapurkar et al. (28)** who demonstrated that the most adverse impacts reported were gastrointestinal symptoms, including diarrhoea, nausea, vomiting, and headaches. No severe adverse effects have been detected in this investigation population.

Our pooled studies for mortality rate reported RR with 95%CI: 0.09 [0.05, 0.13] and, 0.1 [-0.016, 0.232] for fluconazole and itraconazole, respectively. Most reported mortalities are due to immunosuppression, rather than drug-related mortality. Moderate heterogeneity was detected among the pooled studies (chi-square =0.03, I2=67%).

A study by **Lashof et al. (18)** revealed that the rate of mortality on day 42 was comparable between both fluconazole and itraconazole. The fluconazole group had 17 (13%) patients who died, whereas the itraconazole group had 22 (17%) patients who died (P = 0.27). In the fluconazole group, 13 cases (10%) succumbed to malignant disease, while 17 patients (14%) in the itraconazole group died. Non-fungal infectious illnesses resulted in the deaths of one case in the fluconazole group and three cases in the itraconazole group. Three patients in the fluconazole group died of other causes, involving one case who died of candidemia and bacteremia, whereas two cases in the itraconazole group died of other causes. The itraconazole group did not exhibit any systemic fungal infection.

LIMITATIONS

This meta-analysis has several limitations, including heterogeneity among study designs and patient populations, potential publication bias favoring positive results, and inconsistent definitions of clinical and microbiological outcomes. Additionally, limited sample sizes, most studies are old, variations in resistance patterns, and demographic variability may affect generalizability. Comorbidities, follow-up durations, and reporting of adverse events could also confound results. Moreover, a singular focus on fluconazole may overlook the potential benefits of combination therapies.

CONCLUSION

his study documented that fluconazole, irrespective of the route of administration, exhibited significant clinical success and a lower occurrence of adverse events compared to most other antifungal agents in the management of OPC.

Future research should concentrate on examining the long-term efficacy and resistance patterns associated with fluconazole, as well as comparing its effectiveness with emerging antifungal agents across diverse populations and clinical settings. Additionally, further investigation into optimizing the delivery systems of antifungal medications for OPC in immunocompromised patients is warranted

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Conflict of Interest Declaration
The authors declare that they have no affiliations or agreements with any institution or organisation that has a financial interest in the subject matter or material discussed in this manuscript.

Author Contributions
Osamah S. Al Alawi: Conceptualization, methodology design, and final manuscript revision.
Ahmed S. Ali: Conceptualization Literature search, data extraction, statistical analysis, and results presentation. Overall supervision ;Duaa M. Bakhshwin: Risk of bias assessment, synthesis of findings, and discussion writing. Fahad H. Aljahdali: Literature review, methods writing, and final draft coordination. All authors approved the final manuscript.

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