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REVIEW ARTICLE

Antifungal Interventions and Clinical Outcomes: A Review

Simran,[1] Punam Gaba,[1] Neelam Sharma,[1] Jeewanjot Singh[1]

1. Department of Pharmaceutical, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar, Punjab, India.

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Corresponding authors:
SIMRAN SIMRAN
E: simran2002.nov@gmail.com
T: 6284550700

PUNAM GABA
E: punam_gaba@yahoo.co.in

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Abstract

Fungal infections pose a significant risk to public health since they are linked to high rates of illness and death, particularly in immunocompromised individuals. Therapy is difficult because there are few antifungal drugs available and many of them are harmful. Fungi have also evolved defence mechanisms to fight these drugs. This article overlooks at antifungal drugs that are currently on the market, discusses resistance mechanisms and investigates new treatment-enhancing strategies. Combinations of antifungal drugs can increase effectiveness and reduce toxicity. New drug formulations, including nanoparticles are being studied to improve dispersion and reduce adverse effects. Furthermore, commercially marketed prescriptions may become more effective if their chemical makeup is changed. Additionally, novel drugs are being tested more rapidly and precisely using mini-host animal models. These creative methods could expedite the process and enhance patient outcomes. This study notes multiple challenges, such as patient peculiarities, intricate drug interactions and pathogen diversity, while also emphasising the advancements in antifungal therapy. Enhancing efficacy and reducing toxicity requires advancements in diagnosis, treatment and medicine. More studies on emerging fungal infections and antibiotic resistance are needed.

Key words: Drug resistance, fungal; Antifungal agents; Testing; Diagnosis; Mycoses.

Introduction

Aggressive fungal infections are a global issue that result approximately 1.7 million fatalities annually.[1] They are prevalent in immunocompromised patients, as evidenced by their organ transplantation, chemotherapy and/or acquired immune deficiency syndrome.[2] Bearing into consideration Indian data estimations, the annual incidence of mucormycosis may surpass 900,000 cases.[3]

The typical antifungal medications eventually return to the market. In the early 1990s, fluconazole and itraconazole were the first triazole-mediated antifungal medications to be put on the market. Lipid amphotericin B (AMB) formulations were first made commercially available in the middle of the 1990s. In the past, antifungal medications have either made the fungus more resistant or less susceptible.[4] The excessive use of antifungal drugs increases susceptibility to opportunistic infections.[5] Invasive and superficial approaches are available for treating fungal infections affecting the skin or mucous membranes, with dermatophytes and yeasts responsible for most

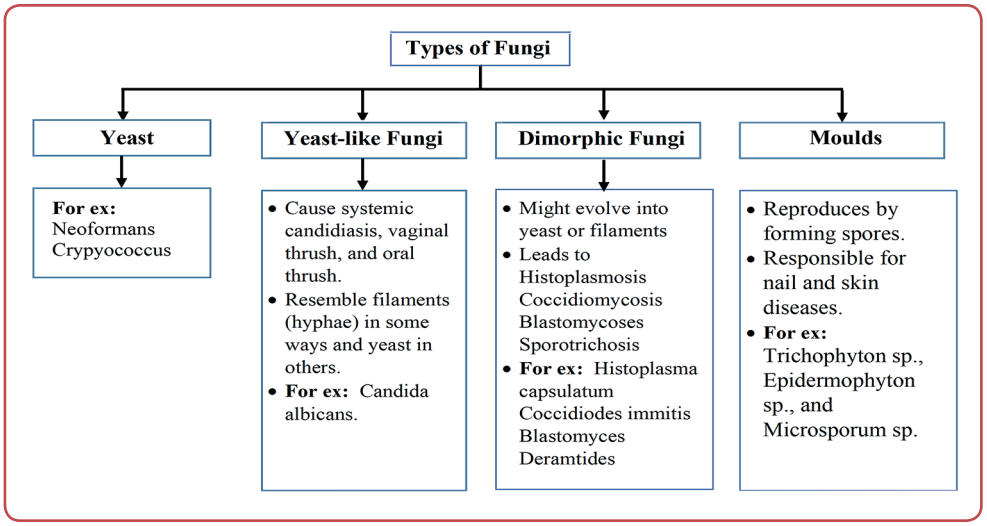


Figure 1: Various types of fungi

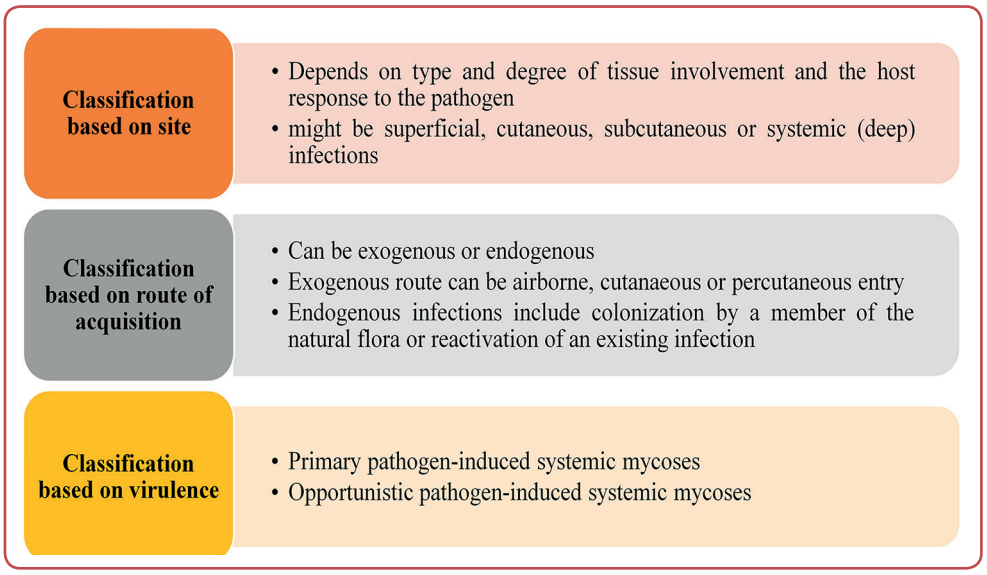


Figure 2: Classification of fungal infection

superficial infections that can occur in the general population and in hospitalised patients (Figure 1). In addition to studying the main approved and carefully chosen experimental antifungal drugs in this study, the article lists the medical applications of both new and older antifungal medications. Those who have indwelling medical equipment, are immunocompromised, or are really ill may become fatally ill from invasive fungal infections (IFIs).[6, 7] Classification of infection is based on level of tissue initially infected as shown in Figure 2.

Challenges for treatment of fungal infections

Since they have their eukaryotic nature, fungi do not belong to many pharmacological targets that can be appropriately addressed for drug development without running the risk of toxicity spanning receptors. Currently available antifungal drugs approved for the treatment of invasive infections fall into only three groups and target a limited number of cellular pathways.

The majority of antifungal drugs either target the body's manufacture of (1,3)-β-D-glucan, an essential component of the fungal cell wall, or the

biogenesis of ergosterol, the functional fungal analogue of cholesterol. If a mycosis infection is resistant to all medications that target the same issue, controlling the infection may become more difficult. According to the medical profession, resistance to all commonly used antifungals is increasing in both clinical and lab settings.[8, 9]

Development of resistance to antifungals

A type of *Candida* is deemed resistant if its minimum inhibitory concentration (MIC) for a particular antifungal drug is higher than the therapeutic breakpoint. Examples of organisms that show intrinsic resistance to antifungals include the majority of isolates of *Candida auris*, *Aspergillus* sp and *Candida krusei* fluconazole resistance is intrinsic. This resistance could be due to either better antifungal extrusion or inefficient drug binding.[9-12] However, the potential for resistance to emerge is a major problem when treating fungal infection. Recent studies have shown an increase in the percentage of resistant fungus. Resistance is seldom brought on by AMB since it does not interact with ergosterol through an enzyme. But occasionally, studies have connected it to species of *Aspergillus* and *Candida*. The resistance of *Candida auris* to AMB has been brought on by point mutations in the genes that regulate the processes that produce ergosterol.[13-15] The gene fluconazole resistance 8 *(FLO8)*, which codes for an unidentified membrane transporter, has also been linked to single nucleotide polymorphisms that cause *Candida auris* AMB resistance.[2, 16, 17] In contrast to other *Aspergilli*, isolates of *Aspergillus terreus* and *Aspergillus flavus* have an inherent resistance mechanism in addition to the alterations shown in the *Candida* species. An increase in catalase levels appears to be linked to this mechanism, which diminishes the oxidative damage caused by AMB.[18, 19] Mutations in the uracil phosphoribosyl transferase (*FUR1*) and cytosine deaminase (*FCY1*) genes are linked to flucytosine-related resistance mechanisms. Reduced conversion of flucytosine into the active metabolite 5FU is linked to mutations in these genes. Additionally, current research show that impairments in repairing DNA mismatches machinery of the fungal cell enhance the likelihood that mutations and, consequently, the emergence of flucytosine resistance in *Cryptococcus* species. Because of the long duration of treatment needed, the serious toxic side effects and the possibility of resistance developing quickly, flucytosine is not recommended as a monotherapy for *Cryptococcus* infections. Another option is AMB, which can permeabilise the membrane and let flucytosine through even at low concentrations. Triazoles and flucytosine have recently been used to treat infections that are difficult to cure and are brought on by species of *Candida* and *Cryptococcus.*[20-22] Overexpression of the efflux pump is linked to a second resistance mechanism. The active efflux of azole medications is made possible by two drug efflux pathways: the major facilitator superfamily (MFS) and the ATP-binding cassette (ABC) families. Protection to antifungals is a result of these pathways. According to earlier research, *Aspergillus fumigatus* responds to voriconazole exposure by upregulating the *CDR1B* gene, which codes for the transporter ABC11. This leads to the development of azole resistance. The *Candida* species also showed similar changes.

Development of novel antifungal

IFIs are much more common now than they were a few decades ago. The primary causes were identified as the rise in immunocompromised patients brought on by autoimmune disorders, cancer, organ transplants, includes the use of prosthetic devices and indwelling catheters.[23-27] In these cases, having potent antifungal medications on hand is crucial. However, some of the limitations of the available antifungal medications that limit the effectiveness of treatment include the development of antifungal resistance, the occurrence of side effects related to the required dosage, the duration of treatment, or the similarity between fungal and mammalian cells.[28, 29] In considering these restrictions, the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) suggested voriconazole as a first-line empirical treatment for invasive aspergillosis and echinocandins as a primary therapy and first-line empirical treatment for suspected invasive candidiasis.[30-32]

Because antifungal drugs are difficult to find and resistance arises, particularly in patients with IFIs who have not responded to antifungal monotherapy, numerous attempts have been made to

use a combination of treatments.[28, 33-35] The safety and effectiveness of the drug may be improved by specific combinations.[36, 37] An assortment of combinations may have a synergistic or additive impact, including caspofungin and flucytosine and AMB, caspofungin and voriconazole and caspofungin and AMB.[38, 39] It actually was recommended to use intravenous AMB in combination with oral flucytosine to prevent and treat opportunistic infections in adults and adolescents with HIV.[19, 34] Many attempts have been made in the last few years to create new antifungal medications.[40] Recently, rezafungin was authorised.[41]

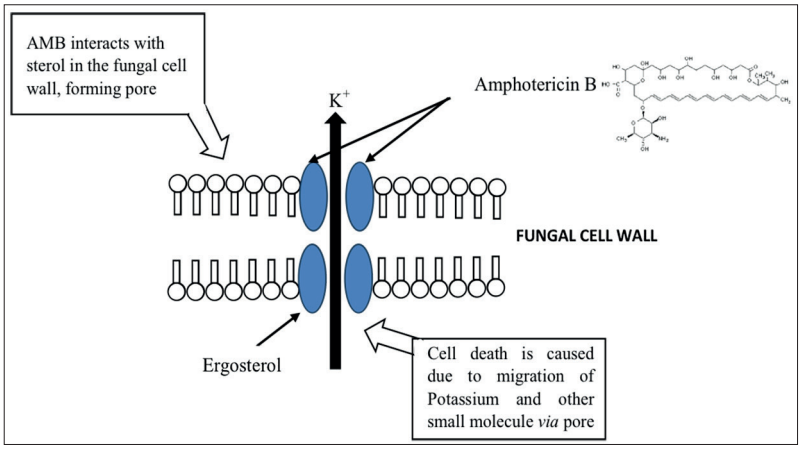
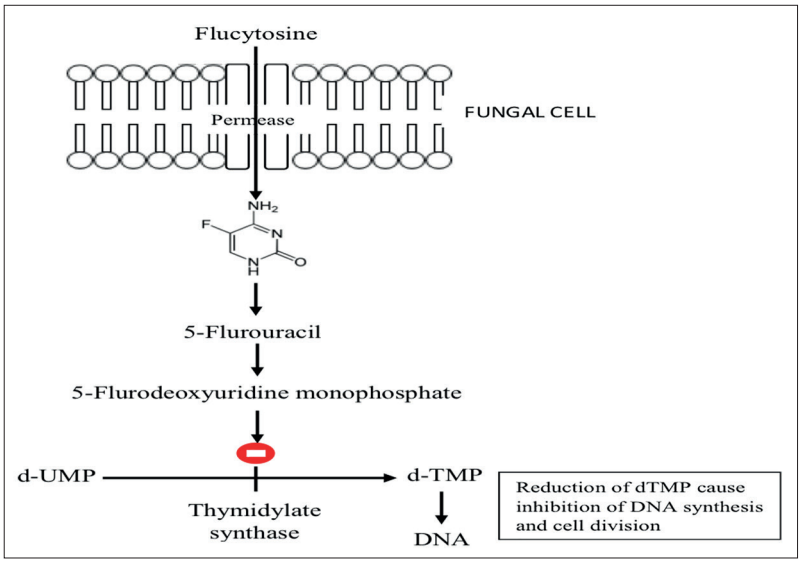
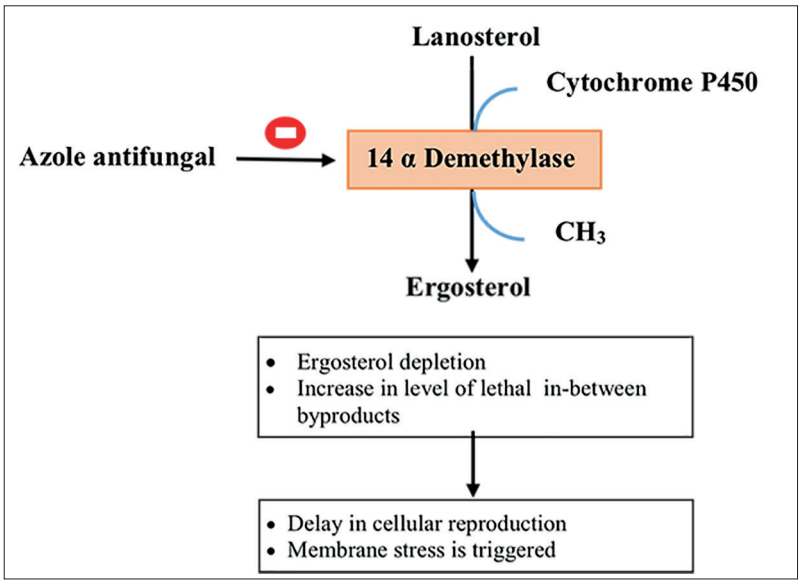
1. Rezafungin was newly granted authorisation. Echinocandin, was initially approved by the Food and Drug Administration (FDA) on 22 March 2023. It is advised for use by people who are at least eighteen years old and have few or no alternative options for treating invasive *candidiasis* and candidemia.[36, 42, 43]
2. Adults and postmenarchal women with vulvovaginal candidiasis are treated with ibrexafungerp, another innovative oral echinocandin. It functions well against the majority of *Candida* species, including *Candida auris* and *Candida krusei*, according to *in vitro* tests. In individuals with recurrent vulvovaginal candidiasis, ibrexafungerp does not result in resistance and is still effective against most fluconazole-resistant *Candida* species, even when administered monthly.[42, 44]
3. The fungicide pharmaceutical "olofim" (formerly known as F901318) inhibits the production of uridine diphosphate sugars (UDP-sugars) and 1,3-β-D-glucan synthase substrates by targeting the enzyme dihydroorotate dehydrogenase. Patients with azole-resistant, invasive, difficult-to-treat aspergillosis, scedosporiosis and lomentosporiosis for which there are few other treatment options are being investigated for olorofim in a phase 2b open-label study. For the treatment of invasive scedosporiosis, invasive aspergillosis, invasive scopulariopsis and cocidioidomycosis, the FDA and European Medicines Agency (EMA) recognised the antifungal drug as an orphan medication.[8, 41, 45, 46]
4. Opelconazole (PC945) is an inhalation triazole that works similarly to other azoles. The lungs are the primary target during inhalation. However, because of formulation changes, opelconazole appears to produce low plasma concentrations, in those who have recurrent vulvovaginal candidiasis, ibrexafungerp does not induce resistance and is effective against most fluconazole-resistant *Candida* species even when administered monthly. Opelconazole was approved by the European Union as an orphan medication to treat invasive aspergillosis on 13 January 2023.[8, 47-50]
5. The FDA authorised the oral tetrazole oteseconazole (VT-1161) on 26 April 2022. It was created with an enhanced safety and efficacy profile in mind and it targets CYP51. *In vitro*, it regularly and successfully combats *Candida glabrata*, fluconazole-resistant *Candida albicans* and *Candida albicans* that cause vulvovaginal candidiasis. According to the CL-011 and CL-012 studies, oteseconazole treated recurrent vulvovaginal candidiasis and prevented acute vulvovaginal candidiasis recurrence with fewer side effects.[51-53]
6. An oral tetrazole called quilseconazole (VT-1129) has shown efficacy against *Cryptococcus* species *in vitro*. Additionally, it was intended to have a higher profile of efficacy and safety. The FDA designated quilseconazole as a qualified infectious disease product and as an orphan drug to treat potentially lethal *Cryptococcus* infections.[54-57]

The FDA has designated Tetrazole VT-1598 as a qualified infectious disease product, granted it orphan drug status and granted it fast-track classification with the goal to efficiently treat coccidioidomycosis. Additionally, VT-1598 exhibits action against *Rhisopus arrhisus*, *Candida auris* and *Aspergillus.*

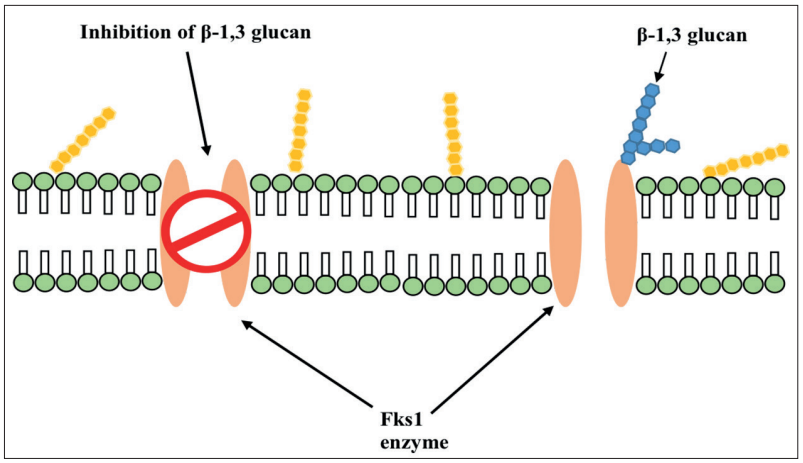
Classification of antifungal agents for clinical purposes

Antifungal agents for clinical purposes are categorised as polyenes, pyrimidines, azoles and echinocandins, as seen in Table 1.

Table 1: Classification of antifungal agents for clinical purposes

Category	Pharmacological pathway	Examples
Polyenes		Amphotericin B (ABM)
Pyrimidines		Flucytosine (5-fluorocytosine)
Azoles		Fluconazole Itraconazole Posaconazole Voriconazole Isavuconazole

Echinocandins



Caspofungin
Micafungin,
Anidulafungin

Discussion of case study findings

The case examples illustrate the wide diversity of fungal infections that are seen in clinical settings, the range of antifungal medications that are used and the range of treatment outcomes and related difficulties (Table 2).

1. The example of providing enteral isavuconazole to a paediatric patient is done as a case study due to the level antifungal therapy need in an immunocompromised child. It necessitates careful consideration of the dosage, route of administration and possible drug interactions. The achievement of the outcome, despite the observed trough concentrations being lower than what was anticipated, signals the effectiveness of enteral administration, but more work is needed to identify the appropriate dose for this group of patients.[58]
2. The case of persistent endogenous fungal endophthalmitis serves as an example of the difficulties in managing profound fungal infections and the significance of modifying therapy in response to clinical response. AMB and voriconazole improved the initial poor response to fluconazole, highlighting the necessity for flexibility in antifungal selection and the possible advantages of combination therapy. The emergence of neovascular glaucoma emphasises the possibility of chronic issues.[59]
3. The limits of depending exclusively on in vitro susceptibility data for formulating treatment strategies are highlighted by the study investigating the predictive usefulness of antifungal susceptibility tests in Cryptococcus neoformans var grubii fungemia. The significance of taking into account additional factors, such as the severity of the disease, comorbidities and treatment duration, is highlighted by the lack of association between the results of susceptibility testing and clinical outcomes.[60]
4. Phaeohyphomycosis caused by *Alternaria infectoria* and *Colletotrichum gloeosporioides* is an example of a fungal disease that is difficult to cure since it is resistant to multiple therapies. The necessity for alternate treatment strategies, like surgery, is highlighted by resistance of *Alternaria infectoria* to all five tested antifungal medications.[6]

Table 2: Case studies

N	Title	Fungal infection	Drug	Mechanism of action	Dosage and administration	Outcomes	Challenges	Ref
1	**Isavuconazole is administered by enteral tube to a child.**	*Aspergillus ustus, Aspergillus fumigatus, Mycobacterium avium* complex and a condition known as	Isavuconazole (ISA)	This wide-spectrum azole antifungal interferes with the formation of ergosterol by blocking lanosterol 14α-demethylase.	200 mg intravenously (IV) every 8 hours for six doses, then 200 mg IV every day; 200 mg gastrostomy tube (G-tube) capsules were thereafter used every day.	Successful treatment of IFI; trough concentrations lower than adult literature suggests.	There is no FDA-approved paediatric ISA dosage and there may be a chance that graft-versus-host disease (GvHD) will reduce absorption.	[58]
2	**Chronic endogenous fungal endophthalmitis**	Endogenous fungal endophthalmitis caused by *Candida albicans*	Fluconazole, amphotericin B (AMB), voriconazole	Fluconazole and voriconazole: inhibit lanosterol 14α-demethylase, interfering with ergosterol biosynthesis. Amphotericin B: binds to ergosterol in fungal membranes.	IV fluconazole initially, then intravitreal (IVT) AMB; continued fluconazole; switched to IVT and topical voriconazole.	Initial poor response to intravenous fluconazole; improved with IVT amphotericin B and topical voriconazole; persistent panuveitis; developed neovascular glaucoma.	Poor initial response to fluconazole; persistent inflammation; development of neovascular glaucoma requiring multiple topical antiglaucoma agents.	[59]
3	**The clinical prognosis of *Cryptococcus neoformans var grubii*. Fungemia has never been predicted by YeastONE antifungal susceptibility testing.**	*Cryptococcus neoformans var grubii* fungemia	The clinical course of *Cryptococcus neoformans var grubii* fungemia has never been predicted by YeastONE antifungal susceptibility testing.	AMB: binds to ergosterol. Remaining drugs: inhibit lanosterol 14α-demethylase. Flucytosine: inhibits DNA synthesis.	AMB with or without fluconazole or flucytosine for induction; IV or oral fluconazole for maintenance.	Antifungal susceptibility testing did not predict clinical outcomes; mortality associated with disease severity, comorbidities and inadequate treatment.	High death rates despite treatment; antifungal susceptibility testing not predictive of outcome.	[60]
4	**Feohifomicosis in a renal transplant patient caused by *Alternaria infectoria* and *Colletotrichum gloeosporioides*.**	*Phaeohyphomycosi* and *Alternaria infectoria*	AMB, itraconazole, flucytosine, fluconazole, voriconazole	AMB: binds to ergosterol. itraconazole, fluconazole, voriconazole: inhibit lanosterol 14α-demethylase. Flucytosine: inhibits DNA synthesis.	Unspecified dosage; susceptibility testing performed, not treatment.	Lesions removed surgically; no relapse.	Only voriconazole and amphotericin B can affect *C gloeosporioides*, but *Alternaria infectoria* is resistant to all five drugs.	[61]

Table 3: Completed clinical trials

NCT No	Study title	Conditions	Age	Phases
NCT01307930	Obesity and/or weight's impact on anidulafungin drug concentrations	Obesity, mycoses	Adult, older adult	4
NCT00300677	To calculate the amount of voriconazole in the brain following two loading doses and three maintenance doses spaced out over three days	Fungal	Adult	4

NCT04035187	Itraconazole oral absorption	Fungal	Adult, older adult	4
NCT04532164	Study to determine whether healthy participants' skin reacts allergically to sunlight when using cream V61-044 to treat fungal infections	Dermatitis, photoallergic	Adult	3
NCT01062165	Impact of obesity and/or weight on caspofungin drug levels	Obesity, fungal	Adult, older adult	4
NCT02631954	Phase I clinical study to compare the pharmacokinetic properties of Vfendâ® IV 200 mg with *Vorico* injection 200 mg (voriconazole) for single dose crossover intravenous infusion in healthy participants	*Aspergillus* infections, *Candida* infections, fungal	Adult	1
NCT04432376	Safety and effectiveness trial of miconazole oil vs vehicle for ear canal fungal infection (otomycosis)	Otomycosis	Child, Adult, older adult	2 3
NCT02142153	F901318 study of single ascending doses in healthy male volunteers	Invasive aspergillosis	Adult	1
NCT01090141	Micafungin drug concentration analysis in volunteers who were overweight, obese and extremely obese	Obesity, nutrition disorders, overweight	Adult, older adult	4
NCT00940017	A study to determine the lung concentration with voriconazole and anidulafungin following intravenous administration in healthy subjects	Aspergillosis, candidemia	Adult	4
NCT01851590	Resin vs amorolfine vs terbinafine treatment in onychomycosis	Onychomycosis	Adult, older adult	4
NCT03098615	Study evaluating the effect of *Jublia* on dermatophytomas	Onychomycosis, dermatophytosis	Adult, older adult	4
NCT03110029	Efinaconazole 10 % solution (*Jublia*): a comparison of patients wearing and not wearing toenail polish to determine its effectiveness and compatibility for treating toenail onychomycosis	Onychomycosis of toenail	Adult, older adult	4
NCT04229303	Phase 1: three-part ZP-059 study on sad, mad and cross-over in participants with and without asthma	Allergic bronchopulmonary aspergillosis	Adult	1
NCT01039584	A randomised investigation assessing the therapeutic equivalence of two formulations of butoconazole nitrate vaginal cream, 2 %	Vulvovaginal candidiasis	Adult, older adult	NA
NCT00830388	Ketoconazole foam 2 % for the treatment of versicolor	Tinea versicolor	Adult, older	4

SAD: single ascending dose; MAD: multiple ascending dose;

An overview of clinical research on the evaluation of drugs and antifungal treatments

Table 3 includes sixteen research studies on fungal infections and associated treatments. Each study examines several antifungal drugs or therapies in relation to various fungal disorders, including obesity, mycoses, onychomycosis and others. Safety, effectiveness, absorption and drug concentrations are the primary research topics. The study includes a number of drug studies for medications like miconazole, anidulafungin, voriconazole, itraconazole and micafungin. Testing therapeutic efficacy, figuring out drug concentrations and analysing absorption under different body states (such obesity) are just a few of the numerous goals of these trials. In this regard, some research examines how fat influences drug concentrations, while others concentrate on particular therapies for fungal infections of the skin, nails or ear canal. The research is conducted in one, two, three, or four phases and involves a wide range of age groups, including children, adults and senior persons. While Phase 2 and 3 trials evaluate the treatment's safety and effectiveness in patients, Phase 1 trials usually

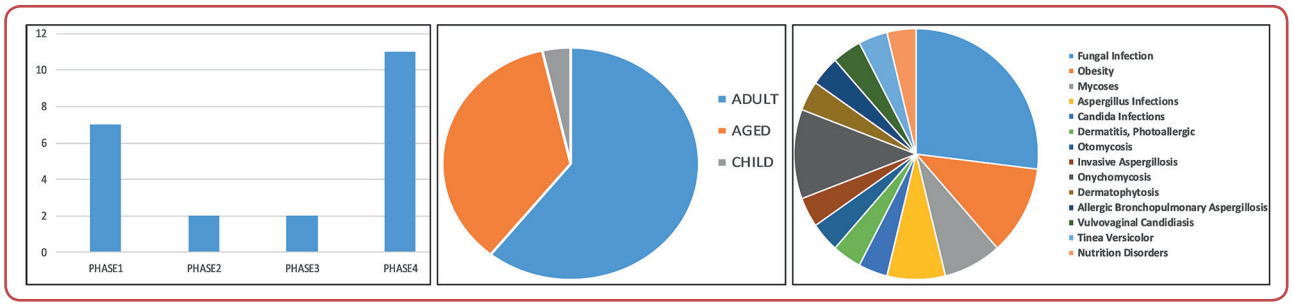


Figure 3: An overview of clinical research on the evaluation of drugs and antifungal treatments

involve healthy volunteers. Additionally, some studies compare various treatments for the same ailment, including tinea versicolor or onychomycosis. This thorough approach to fungal therapy research reveals the most effective treatment for fungal infections (Figure 3).[62-64]

Emerging trends and future directions

Many emerging factors are influencing the direction of antifungal therapy. The increasing occurrence of drug-resistant fungal species is driving the demand for novel antifungal medications with distinct mechanisms of action. The range of possible treatments has increased with the creation of new antifungal classes, such echinocandins and enhanced forms of already-approved medications, like liposomal AMB. To improve efficacy and lower the risk of drug resistance, combination therapy is being utilised more and more. Research is also being done on targeted treatments, such as those that target particular fungal virulence factors. Natural materials like eugenol are being investigated for their potential as sources of new antifungal medications. For fungal infections to be identified earlier and with greater accuracy, better diagnostic technologies are required. Additionally, more study is required to improve treatment plans for particular patient groups, such as newborns and immunocompromised people. The upsurge in fungal infections linked to COVID-19 emphasises how crucial it is to comprehend how viral and fungal illnesses interact and create effective management plans. [65, 66]

Conclusion

Antifungal drugs are critical to the treatment of fungal diseases, which are becoming more common. Novel antifungal drugs and strategies are needed to address the increasing problem of drug resistance and to improve patient outcomes. Ongoing study of drug efficacy, side effects and resistance patterns will be important to ensure the full effectiveness of antifungal treatments. Clinical practice relies heavily upon antifungal medicines because fungus infections are one of the fastest-growing types of infectious disease worldwide, often linked to older populations, immune-challenged individuals and emerging and/or re-emerging fungi. As the landscape of fungal diseases evolves, it's critical to maintain a balance between restricting the risk of developing resistance and delivering effective treatment. Despite these improvements in antifungal treatment, problems remain. Furthermore, the limited number of antifungal classes and the toxicities they are associated with necessitate careful selection and monitoring. New drug classes and other therapeutic approaches, like combination therapy and the development of new biological targets, hold promise for getting around these limitations. Additionally, exploring the potential of precision medicine—where antifungal drugs are tailored to a patient's particular infection—may improve treatment outcomes. Ultimately, in order to solve the issue of antifungal resistance and enhance patient care, a multimodal approach involving researchers, medical practitioners and public health officials is required. Sustained efforts to improve antifungal management and a commitment to developing innovative treatment options will be necessary for future success in treating fungal diseases. In

order to treat fungal infections and improve quality of life, it is imperative to refine existing chemicals, develop new formulations and employ alternative therapies for both prevention and therapy. In addition to describing advancements in antifungal therapy, this page discusses a variety of diseases, complicated medications and patient features. For efficacy and reduced adverse effects, new medications, better techniques and enhanced diagnostics are required. Treatment resistance and other fungal risks require more investigation.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Simran (S):
0009-0004-8319-218X
Punam Gaba (PG):
0000-0003-4528-0440
Neelam Sharma (NS):
0000-0003-1198-7085
Jeewanjot Singh (JS):
0009-0000-6290-9250

Author contributions

Conceptualisation: S
Formal analysis: S
Investigation: S
Data curation: S
Writing - original draft: S, PG
Writing - review and editing: PG, NS, JS
Supervision: PG, NS.

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