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Review

Antifungal pipeline: New tools for the treatment of mycoses

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ABSTRACT

Fungal infections are becoming an escalating public health challenge, particularly among immunocompromised individuals. The partially limited efficacy of current antifungal treatments, their potential adverse effects, and the increasing problem of resistance emphasize the need for new treatment options. Existing antifungal classes—allylamines, azoles, echinocandins, polyenes, and pyrimidine analogs—face challenges due to their similarity with human cells and rising resistance.

New antifungal agents, such as ibrexafungerp, rezafungin, oteseconazole, and miltefosine, offer novel mechanisms of action along with reduced toxicity. While antifungal resistance is a growing global concern, fungal infections in low- and middle-income countries (LMICs) present specific challenges with high rates of opportunistic infections like cryptococcosis and endemic mycoses such as histoplasmosis. The World Health Organization's fungal priority pathogens list highlights the prevalence of these infections in LMICs, where limited access to antifungal drugs and misuse are common.

This review provides a comprehensive overview of these new agents and their mechanisms, and explores the challenges and roles of antifungal drugs in LMICs, where the burden of fungal infections is high. Continued research and development are essential to address the rising incidence and resistance of fungal infections globally.

Fármacos antifúngicos en desarrollo: nuevas herramientas para el tratamiento de las micosis

Palabras clave:
Nuevos antifúngicos
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Miltefosina
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RESUMEN

Las infecciones fúngicas se han convertido en un problema creciente en el ámbito de la salud pública, especialmente entre aquellos pacientes con inmunodeficiencias. La limitada eficacia de los tratamientos antifúngicos actuales, sus potenciales efectos adversos y los cada vez mayores problemas de resistencia reflejan la necesidad de nuevas opciones terapéuticas. Las diferentes clases de antifúngicos – alilaminas, azoles, equinocandinas, polienos y análogos de la pirimidina – tienen, en ocasiones, como dianas terapéuticas moléculas presentes en las células humanas, un problema que se suma al aumento de la resistencia.

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MAT2203
ATI2307
GR2397
NP339
PRMB
Países de renta media y baja

Nuevos agentes antifúngicos, como el ibrexafungerp, la rezafungina, el oteseconazol y la miltefosina, ofrecen nuevos mecanismos de acción, al mismo tiempo que una menor toxicidad. Mientras que la resistencia antifúngica es un problema global creciente, las infecciones fúngicas en países de renta media y baja (PRMB) presentan retos específicos, con altas tasas de infecciones oportunistas, como la criptococosis, y micosis endémicas como la histoplasmosis. El listado de los patógenos fúngicos más importantes según la Organización Mundial de la Salud resalta la prevalencia de esas infecciones en PRMB, donde el acceso a los antifúngicos y un mal uso de ellos son circunstancias habituales.

Esta revisión ofrece una visión general de los nuevos agentes y sus mecanismos, y explora los retos y el papel de los antifúngicos en los PRMB, donde la carga que conlleva las infecciones fúngicas es elevada. La investigación y el desarrollo continuados son esenciales para hacer frente al aumento de la incidencia y de la resistencia de las infecciones fúngicas a los tratamientos en todo el mundo.

Fungal infections, once considered rare, now pose a significant public health challenge, and our arsenal for diagnosis and treatment is limited.[23,25,129] Several factors contribute to this rise including the widespread use of chemotherapy for cancer, immunosuppression for organ transplantation, expanded access to intensive care units, other immunosuppressing conditions such as diabetes, and the recent coronavirus disease 2019 (COVID-19) pandemic.[9,54,49] These conditions and advances in treating underlying diseases result in a compromised immune system, making individuals more susceptible to fungal infections.[36,64,73,89,100] Antifungals play a crucial role in treating fungal infections, yet their effectiveness is tempered by limited effectiveness in subpopulations like morbidly obese patients or patients receiving extra corporal membrane oxygenation (ECMO), adverse effects, issues with long term tolerability, and the emergence of resistance.[7,19,36,50,61,63,70,100,115]

While Europe is generally well-prepared to manage invasive fungal infections, some institutions lack access to essential diagnostic tools and antifungal drugs, despite their classification as essential by the World Health Organization (WHO).[102] For example, Italy faces restricted access to therapeutic drug monitoring,[123] whereas Austria is well-equipped, with all antifungal agents available according to hospitals participating in the survey.[103] In Asia-Pacific, resources for diagnosis and treatment vary widely, with economic and geographic factors influencing the management of the disease burden.[101]

In low- and middle- income countries (LMICs), additional barriers contribute to the increasing prevalence of fungal infections. These include global socio-economic challenges, limited availability of fungal diagnostics and antifungal medications, and improper use of existing treatments.[25,65,94,98,101,102,108]

The primary pathogens responsible for human fungal infections are *Candida*, *Cryptococcus neoformans*, *Aspergillus*, and those causing endemic mycoses, including *Histoplasma capsulatum*.[17,94] However, infections by Mucorales, *Fusarium* species and other rare molds that often show intrinsic resistance to many classes of antifungals continue to emerge.[43,59,56,51,62] Antifungal therapy has made remarkable advances in recent decades, but despite increased awareness and the development of new antifungal drugs, morbidity and mortality from fungal infections continue to increase.[23]

Based on their mechanisms, five classes of antifungal drugs are available at the moment. Polyenes (e.g. amphotericin B) selectively target membrane sterols like ergosterol, disrupting essential membrane functions and leading to cell death,[18] with lipid formulations showing improved tolerability.[53] Triazoles (e.g., fluconazole or voriconazole) inhibit the 14α-lanosterol demethylase, an enzyme essential for ergosterol synthesis in fungi, thereby disrupting cell membrane integrity and function.[41,61] Echinocandins (e.g. caspofungin) target 1,3-β-glucan synthase, an enzyme, which is critical for a proper cell wall formation, leading to cell lysis and death due to the loss of structural integrity.[57,114] Allylamines (e.g. terbinafine) inhibit the ergosterol synthesis pathway by targeting squalene epoxidase, an enzyme at the beginning of the pathway. This leads to an accumulation of squalene and a lack of ergosterol in the fungal cell membrane.[121] Pyrimidine analogs (e.g., flucytosine) inhibit DNA and RNA synthesis by mimicking natural nucleotides, disrupting the fungal cell's ability to replicate and synthesize essential proteins, leading to cell death.[88]

One of the primary challenges in developing antifungal drugs is that fungi, as eukaryotes, share many cellular similarities with humans. This makes it difficult to identify antifungal targets that can be selectively inhibited without causing harmful side effects in patients. Additionally, fungal species are developing resistance to antifungal drugs, complicating treatment efforts even with combination therapies targeting multiple cellular pathways.[116] To date, the most important examples of resistance to antifungals include the emergence of multidrug resistant *Candida glabrata* and *Candida auris*, as well as azole-resistant *Candida parapsilosis* and *Aspergillus* infections.[19,58,69,78]

Antifungal mechanisms encompass a variety of strategies to combat fungal infections. Antifungal agents target fungal cells through different mechanisms, like efflux pumps, inhibition of virulence factors such as biofilms and hyphae, and disruption of fungal enzymes, metabolism, mitochondria and cell wall.[4,88]

There are promising new antifungal drugs in the pipeline that aim to address these issues with novel drug targets and reduced adverse effects. Examples of new/repurposed drugs that have been recently approved for clinical use include ibrexafungerp, rezafungin, oteseconazole and miltefosine,[13,55,52,78] while other new drugs like fosmanogepix, olorofim or opelconazole are currently evaluated in phase 3 clinical trials.[58,69]

This review aims to explore the mechanisms of action of these new antifungal drugs, highlighting both approved agents and those still in development. Additionally, we will focus on the roles and challenges of using antifungal drugs in LMICs, where the burden of fungal infections is often greatest.

Current situation and recently approved antifungals

Several new antifungal drugs have been recently approved, with new mechanisms of action and improved activity against fungal pathogens. This could address current limitations in treatment, such as the need for prolonged hospitalization[28] and frequent administration of medication. The main already approved new antifungals include ibrexafungerp, rezafungin, oteseconazole and miltefosine,[55] which represent important additions to the longer established antifungals.

Ibrexafungerp

Ibrexafungerp (formerly SCY-087 and MK-3118) represents a novel antifungal belonging to the class of triterpenoids, that offers the advantage of oral bioavailability compared to echinocandins.[3,5]

The substance disrupts fungal cell wall synthesis by targeting β-(1,3)-D-glucan synthase, which leads to a decrease in β-(1,3)-D-glucan polymers, weakening the fungal cell wall.[37,77] The mechanism is similar to echinocandins, but ibrexafungerp interacts differently with the target cell. Echinocandins target the catalytic subunit of the enzymatic (1,3)-β-D-glucan synthase, which is encoded by the *FKS* gene, while ibrexafungerp has a different chemical structure and inhibits enzyme activity indirectly by interfering with another site involved in synthesis, disrupting the formation of 1,3-β-glucan.[66] This disruption compromises the integrity of the fungal cell wall, ultimately leading to fungal cell death.[66]

Ibrexafungerp is highly active against various fungal species, including species of *Candida* and *Aspergillus*. It displays a low minimum inhibitory concentration (MIC) in acidic pH, making it superior to azoles and echinocandins.[5] Ibrexafungerp is reported to be generally safe and well tolerated, with few gastrointestinal adverse effects.[5,8] It is available as an oral formulation with an intravenous version in development.[39] Ibrexafungerp has a good oral absorption and a mean half-life of 20–30 h, supporting a once-daily dosing strategy.[20] It was approved by the Food and Drug Administration (FDA) in 2021 for the treatment of vulvovaginal candidiasis (VVC).[32]

The CARES study (clinicaltrials.gov Identifier: NCT03363841), a multicenter, open-label, single arm study, evaluated the efficacy, safety, tolerability and pharmacokinetics of oral ibrexafungerp as an emergency use treatment for patients aged 18 years or older with a documented *C. auris* infection. Enrolment in the study required a documented candidiasis, including candidemia, caused by *C. auris*. The study included a screening visit, up to 11 treatment visits, a follow-up visit, and two follow-up contacts. Results of the study have been made available as interim data and show strong clinical activity of oral ibrexafungerp. Analysis of the data showed that 80% of patients with invasive candidiasis and candidemia experiences a complete response. The treatment was generally well tolerated, with the most common adverse events being gastrointestinal issues. Overall, the initial data are positive and consistent with the previously reported interim results.[107]

Another two studies on the safety and efficacy of ibrexafungerp were conducted, but the final results are not yet available. The first study, FURI (clinicaltrials.gov Identifier: NCT03059992) is a multicentre, open-label, single-arm trial evaluating the efficacy and safety of ibrexafungerp in patients aged 18 years and older with a documented invasive and/or severe fungal disease that had been intolerant or refractory to standard antifungal treatment. Participants were treated with ibrexafungerp for up to 180 days, with options for extended treatment and combination therapy under specific conditions. Enrolment required proven or probable fungal disease and documented failure, intolerance, or toxicity to standard treatments. The study included up to 15 treatment visits, a follow-up visit, and two follow-up contacts. Interim results confirmed positive clinical activity of oral ibrexafungerp in patients with difficult-to-treat, severe, mucocutaneous and invasive fungal infections, including those caused by resistant strains.[107]

The second study, SCYNERGIA (clinicaltrials.gov Identifier: NCT03672292), is a multicenter, randomized, double-blind phase II study, investigating the safety and efficacy of the coadministration of ibrexafungerp with voriconazole in patients with invasive pulmonary aspergillosis. The study was terminated because of slow enrolment during COVID-19.

The ongoing MARIO study (clinicaltrials.gov Identifier: NCT05178862) is a phase III, multicenter, randomized, double-blind study of two treatment regimens for invasive candidiasis, including candidemia. The study involves participants receiving intravenous echinocandin followed by oral ibrexafungerp, versus intravenous echinocandin followed by oral fluconazole. Enrollment of the study has been paused after the sponsor identified a potential cross-contamination risk with a non-antibacterial beta-lactam drug in the manufacturing process. Data collection, which was originally scheduled to be completed by the end of 2024, is expected to resume in 2025.

Ibrexafungerp is expected to fill a gap in oral antifungal therapy, offering an alternative to intravenous echinocandins, with fewer contraindications, drug interactions and resistance issues. The drug shows promise in combination therapy for resistant invasive pulmonary aspergillosis and has potential applications in the treatment of a variety of fungal infections, including candidemia, invasive candidiasis, VVC and invasive aspergillosis. In addition, its oral formulation makes it a more convenient option for patients, especially those requiring long-term antifungal treatment.[52]

Rezafungin

Rezafungin (formerly SP3025 and CD101), derived from its structural analog anidulafungin, an echinocandin, was developed to reduce pharmacological and stability problems of first-generation echinocandins by structural changes. The substance inhibits fungal cell wall synthesis by targeting the enzyme complex (1,3)-β-D-glucan synthase, encoded by *FKS1* and *FKS2* genes.[40,119] Rezafungin and anidulafungin share the same side chain and a similar cyclic core. However, in rezafungin, the hemiaminal region of the echinocandin cyclic nucleus is replaced with a choline aminal ether. This modification reduces the chemical degradation that typically occurs at the hemiaminal region in anidulafungin, thereby enhancing the stability and solubility of rezafungin.[40] As a result rezafungin shows minimal CYP450 interaction,[87] with a plasma half-life of 80 h after the first dose and about 150 h after the second or third dose, allowing once-weekly administration, better tissue penetration and improved safety.[40,105] On January 6th 2021 the European Medicines Agency (EMA) accepted rezafungin for the treatment of invasive candidiasis in adults.[29] The application was supported by data from the phase III clinical study ReSTORE (clinicaltrials.gov Identifier: NCT03667690), which indicated that rezafungin, when administered once weekly, was statistically comparable in effectiveness to the standard treatment of caspofungin, which requires daily dosing. In addition, rezafungin was generally well tolerated and had a similar safety profile to caspofungin.[74,118] Rezafungin received on March 22nd 2023 its FDA approval in the USA for the treatment of candidaemia and invasive candidiasis in patients aged 18 years or older who have limited or no alternative treatment options. The approval is based on limited clinical safety and efficacy data.[34]

Rezafungin is effective against various *Candida* species, including *Candida albicans*, *Candida dubliniensis*, *Candida krusei*, and *Candida tropicalis*, as well as *Aspergillus* spp.; however, Basidiomycota, Mucorales, *Fusarium* species, and species within the family Ajellomycetaceae exhibit intrinsic resistance to rezafungin.[40]

The effects of rezafungin are currently being investigated in three ongoing studies. All three studies are in the recruitment phase. The first study (clinicaltrials.gov Identifier: NCT05534529) is a phase 1, multicenter, open-label study to evaluate the pharmacokinetics, safety and tolerability of a single intravenous dose of rezafungin in pediatric subjects receiving systemic antifungals as prophylaxis for invasive fungal infection or to treat a suspected or confirmed fungal infection. The study is currently not recruiting participants because it has been suspended due to strategic reasons. The second study (clinicaltrials.gov Identifier: NCT05835479) is a phase 2, proof-of-concept, multicenter, open-label randomized, active-controlled study to evaluate the efficacy, safety and tolerability of rezafungin combined with 7 days of co-trimoxazole versus co-trimoxazole monotherapy in HIV-infected adults with *Pneumocystis jirovecii* pneumonia. The last study (clinicaltrials.gov Identifier: NCT04368559, ReSPECT) is a phase 3 study, investigating

the efficacy and safety of intravenous rezafungin in the prevention of invasive fungal diseases in subjects undergoing allogeneic blood and marrow transplantation compared to the standard therapy (fluconazole or posaconazole).

Oteseconazole

Oteseconazole (formerly VT-1161) was first approved by the FDA in 2022 for females with a history of recurrent vulvovaginal candidiasis (RVVC) who are not of reproductive potential.[33] This newly introduced tetrazole antifungal is a member of the azole class and represents a new generation of fungal CYP51 inhibitors. It inhibits ergosterol biosynthesis via 14α-demethylase, similar to other azoles, and has a higher affinity for fungal CYP51 compared to human enzymes, which reduces side effects and drug interactions. It is effective against various *Candida* spp., including resistant strains, as well as dermatophytes and selected Mucorales species.[55,124] In antifungal activity tests against various *Candida* spp., oteseconazole displayed significantly better activity, being over 40 times more potent on average than fluconazole for most species.[113] Particularly for fluconazole-resistant *C. glabrata*, the minimal inhibitory concentration (MIC) of oteseconazole was 64 times lower than that of fluconazole.[106] Oteseconazole shows promise for treating *Candida* infections on mucosal surfaces and nails, particularly for RVVC and onychomycosis. Although oteseconazole has potent activity against RVVC, some limitations must be noted. Oteseconazole has a very long median half-life of 138 days.[112] It is contraindicated in pregnant women and females of reproductive potential due to the risk of fetal harm. It is also contraindicated in lactating women, despite the lack of data on its presence in milk or effects on milk production. No adverse effects were reported in breastfed infants, but the limited follow-up duration prevents definitive conclusions.[112] It is only available orally, and there are no current plans to develop it for invasive candidiasis.[55]

Miltefosine

Miltefosine, originally developed as an anti-cancer medication and FDA-approved in 2014,[31] is an alkyl phospholipid effective against the neglected tropical diseases leishmaniasis.[91] Miltefosine's physicochemical properties, such as being hygroscopic and requiring subzero storage temperatures, have been extensively studied, highlighting its unique structural characteristics and solvate forms.[45] Moreover, research indicates that miltefosine not only directly kills parasites but also modulates host immunity, showing potential in treating allergic diseases by regulating eosinophilic inflammation.[2] It exhibits broad antifungal activity against various yeasts, including *Candida* species and drug-resistant strains. While the exact mechanisms of its action remain incompletely understood, miltefosine induces apoptosis and increases reactive oxygen species production in fungi like *C. krusei* and *Cryptococcus* spp.[55,130] Administered orally, it shows gastrointestinal toxicity and teratogenicity, limiting its use. Clinical studies for candidiasis treatment are lacking, but nanocarrier formulations show promise.[55]

New drugs under clinical development

New antifungal agents are currently in development to address the limitations of existing substances, which include issues such as toxicity, suboptimal pharmacokinetic profiles, potential drug-drug interactions, limited clinical effectiveness, and the problem of emerging antifungal resistance. These new therapies aim to improve treatment outcomes by targeting novel mechanisms of action while minimizing adverse effects and combating resistance challenges.

Opelconazole

Opelconazole (PC945) is a novel triazole antifungal agent designed for inhalation delivery, showing potent activity against *Aspergillus* and *Candida* species, including multi-drug-resistant strains.[52,81] The substance is delivered directly to the lungs by inhalation, providing high local concentrations at the site of infection. This enhances its efficacy against pulmonary infections while minimizing systemic exposure and adverse effects.[81]

In vitro, the substance was shown to tightly bind and thereby inhibit lanosterol 14α-demethylase (CYP51A1 and CYP51B). This enzyme is crucial for the biosynthesis of ergosterol, an essential component of the fungal cell membrane needed to maintain membrane integrity and function. By blocking the enzyme, opelconazole disrupts the production of ergosterol synthesis, leading to the accumulation of toxic sterol intermediated and subsequent disruption of the fungal cell membrane. This disruption causes cell membrane instability, increased permeability, and ultimately, fungal cell death.[52,81] Preliminary results showed that opelconazole was well-tolerated and helped reduce fungal burden in the lungs, potentially offering a significant therapeutic benefit for lung transplant patients at risk of aspergillosis.[90] The ongoing OPERA-T study (NCT05238116) is investigating the safety and efficacy of opelconazole in combination with other antifungal therapy for the treatment of refractory invasive pulmonary aspergillosis. To date no results are available.

Olorofim

Olorofim (F901318) is a novel antifungal and belongs to the class of orotomides. Its mechanism of action involves the inhibition of the fungal dihydroorotate dehydrogenase (DHODH), an enzyme essential for DNA synthesis. The drug shows no activity against human DHODH, resulting in limited toxicity and a favorable safety profile.[86] It is orally available, effective against triazole-resistant and multi-resistant fungi,[60] but has poor water solubility and high protein binding. However, it is well distributed in tissues, including the kidney, liver, lung, and even the brain at low concentrations. Olorofim is a weak CYP3A4 inhibitor, making it prone to drug-drug interactions.[67,120] Prolonged exposure leads to a delayed fungicidal effect.[26]

In vitro, olorofim shows broad-spectrum activity against fungi like *Aspergillus* spp., *H. capsulatum*, and *Fusarium* spp.[86] It is highly active against pathogenic *Aspergillus* species, including azole-resistant strains, with MICs < 0.1 μg/mL, outperforming amphotericin B, voriconazole, and posaconazole.[14,60,99] Resistance to this agent is not easily induced as observed for *Aspergillus fumigatus*.[86] No cross-resistance with azole-resistant *Aspergillus* species was observed.[96] However, it is not effective against *Candida* spp., *C. neoformans*, and Mucorales due to differences in DHODH.[86]

In vivo, olorofim demonstrated strong efficacy in murine models of invasive aspergillosis, including wild-type and azole resistant strains.[60,72,86] It significantly extended survival, with up to 88% survival in mice infected with *A. fumigatus*, *Aspergillus nidulans*, and *Aspergillus tanneri*.[109] In immunosuppressed mice with *Aspergillus flavus* infections, olorofim lowered galactomannan levels and cleared lung tissue.[83]

The recently completed FORMULA-OLS study (NCT03583164) investigated olorofim as a treatment for invasive fungal infections in patients with limited options. This open-label, single-arm study focused on infections caused by *Lomentospora prolificans*, *Scedosporium* and *Aspergillus* species, and other resistant fungi susceptible to olorofim. Key findings of the study were that olorofim had a

median dosing duration of 84 days, extending to 308 days for some patients. It showed a positive risk-benefit profile, with 44% of patients achieving a complete or partial response by day 42 and an overall response rate of 69%. All-cause mortality was 15% at day 42 and 20% at day 84. Olorofim was generally well tolerated, with 8% of patients experiencing serious adverse events, including drug-induced liver injury, and 2% requiring discontinuation. Non-serious adverse effects included diarrhea, nausea, and vomiting. Olorofim is the only antifungal with Breakthrough Therapy Designation from the US FDA.

The ongoing OASIS Phase III study (NCT05101187) is evaluating the efficacy, safety, and tolerability of olorofim compared to liposomal amphotericin B and standard care in patients with invasive aspergillosis who are resistant to or unsuitable for azole therapy. The study is expected to be completed by 2026.

Fosmanogepix

Fosmanogepix is a water-soluble phosphate prodrug that can be administered intravenously or orally and is metabolized into its active form, Manogepix (APX001A, formerly E1210), by systemic alkaline phosphatases.[47] The drug inhibits the fungal enzyme Gwt1, which is crucial for linking mannoproteins to the fungal cell wall. By targeting this enzyme, fosmanogepix disrupts the integrity of the fungal cell wall, leading to cell death.[48] Fosmanogepix is highly selective and specific to fungi and does not inhibit the closest human ortholog of Gwt1, the phosphatidylinositol glycan anchor biosynthesis class W (PIG-W) protein.[125] The drug displays broad-spectrum activity against *Candida* species, including *C. auris*, which is known for its resistance to many antifungal drugs.[122] In addition, it is effective against *Aspergillus*, *Cryptococcus*, *Fusarium* and *Scedosporium* species.[6] However, it lacks activity against certain species like *C. krusei* and *Candida inconspicua*.

The efficacy of fosmanogepix has been evaluated in several in vivo models of invasive fungal infections, including disseminated infections (*C. albicans*, *C. glabrata*, *C. auris*, *C. neoformans*, *Fusarium solani*) and pulmonary infections (*Aspergillus* spp., *Scedosporium prolificans*, *Rhizopus* spp.). In addition to demonstrating increased survival, several murine and rabbit infection models showed a reduced fungal burden in the lungs, kidneys, eyes, spinal cord, and brain.[48] Phase I and II trials showed safety and efficacy for the treatment of invasive candidiasis with promising treatment success and very low toxicity.[15,52]

A phase III trial is underway comparing the safety and efficacy of fosmanogepix for the treatment of candidemia and/or invasive candidiasis with standard therapy using caspofungin and optional fluconazole (NCT05421858).

MAT2203

MAT2203 is a novel oral formulation of amphotericin B utilizing a proprietary lipid nanocrystal delivery system. This system safely transports the drug from the gastrointestinal tract to the bloodstream, effectively targeting both mucosal and systemic fungal infections while minimizing toxicity.[44,55] The medication demonstrated efficacy in treating murine aspergillosis,[22] murine cryptococcal meningoencephalitis,[76] and human cryptococcal meningitis.[12] Another research study showed the in vivo effectiveness of MAT2203 in managing pulmonary infections caused by *Rhizopus delemar* or *Mucor circinelloides f. jenssenii* in immunosuppressed mice. Treated animals exhibited extended median survival, improved overall survival rates, diminished tissue fungal load, and enhanced histological lung architecture in infected areas.[44]

Phase I studies of MAT2203 showed gastrointestinal side effects but preserved renal function.

Two clinical trials – one for the treatment of chronic mucocutaneous candidiasis and one for the treatment of moderate to severe VVC – showed clinical improvements, promising tolerability and systemic antifungal exposure, but efficacy in mucocutaneous candidiasis remains suboptimal.[55] The most recent study (clinicaltrials.gov Identifier: NCT05541107) evaluates the effectiveness and safety of step-down induction and consolidation therapy for treating cryptococcal meningitis. This will involve comparing oral MAT2203 combined with flucytosine to standard care therapy. Further research is needed to optimize dosing and explore its potential in combination therapy and prophylaxis. If approved, MAT2203 could play a role in candidiasis management.

ATI2307

ATI2307 is an aromatic diamidine, similar to pentamidine and furamidine that disrupts mitochondrial membrane potential.[55] The drug selectively disrupts yeast mitochondrial function through the inhibition of the respiratory chain complexes III and IV, leading to a decrease in intracellular ATP levels in the cells. This mechanism is distinctively targeted at fungi like *C. albicans* and *Saccharomyces cerevisiae*, as demonstrated by its minimal impact on mammalian mitochondrial function.[111,131] The antifungal has shown in vitro effectiveness against *Candida* species, such as *C. albicans*, *C. glabrata*, and azole- and echinocandin-resistant *C. auris* strains. It has also demonstrated activity against *Cryptococcus* spp.[128] Research conducted on immunosuppressed rabbits infected with *C. neoformans* showed a decrease in fungal load in the cerebrospinal fluid and brain tissue compared to the control group.[42] The novel antifungal exhibits potent activity against yeasts and filamentous fungi and could be a useful treatment for fungal infections. Since there is a lack of human study data at present, limited information exists regarding the clinical effectiveness and safety of the medication.

GR2397

The antifungal agent GR2397 (formerly VL-2397) is a non-ribosomally synthesized cyclic hexapeptide with a structure similar to the siderophore ferrichrome isolated from the Malaysian leaf litter fungus *Acremonium persicinum* MF-347833.[82] The antifungal activity of GR2397 relies on uptake via a specific siderophore iron transporter SIT1, limiting its activity to SIT1-positive strains like *C. glabrata* and *Candida kefyr*, while *C. albicans* is resistant.[24] The exact antifungal mechanism is still unclear.[110]

Phase I studies indicate good tolerability up to 1200 mg in healthy volunteers and no serious adverse events. A phase II trial, comparing GR2397 to standard treatment for invasive aspergillosis (clinicaltrials.gov Identifier: NCT03327727) was terminated in early 2019 due to business reasons.[110] To date no further studies are available. Its narrow spectrum suggests a targeted role in treating *C. glabrata* and *C. kefyr* infections. Its renal excretion may also be advantageous for urinary tract infections caused by *C. glabrata*.[55]

NP339

NP339, a novel 2-kDa polyarginine peptide, exerts its antifungal activity through a charge–charge-initiated membrane interaction, specifically targeting the fungal cell membrane.[27] This unique mechanism of action, distinct from existing antifungal classes, allows NP339 to exhibit rapid fungicidal activity against various fungi, including species of *Candida* and *Aspergillus*, without inducing resistance or cross-resistance to other antifungals. NP339 is non-cytotoxic, non-hemolytic, and has shown efficacy in murine models of candidiasis and other systemic and mucocutaneous fungal infections.[27,52] The differentiated safety and toxicity profile of NP339, along with its innovative mechanism of action, positions it

Table 1
Overview of new antifungal drugs and mode of action.

Drug	Mechanism of action	Targeted fungi
ATI2307	Disruption of mitochondrial function	*Candida*, *Cryptococcus*
Fosmanogepix	Inhibition of fungal enzyme Gwt1, disruption of linking mannoproteins to fungal cell wall	*Aspergillus*, *Candida*, *Cryptococcus*, *Fusarium*, *Coccidioides immitis*, *Histoplasma capsulatum*
GR2397	Targeting of fungal cell membrane, mechanism not fully understood	*Candida*, *Aspergillus*
Ibrexafungerp	Inhibition of β-(1,3)-D-glucan synthase, disruption of fungal cell wall formation	*Candida*, combination therapy against *Aspergillus*
MAT2203	Inhibition of ergosterol synthesis by binding to ergosterol	*Candida*, *Aspergillus*, *Cryptococcus*
Miltefosine	Disruption of cell membrane integrity and mitochondrial function	*Candida*, *Cryptococcus*
NP339	Targeting of fungal cell membrane by charge-charge-initiated interaction	*Candida*, *Aspergillus*
Olorofim	Inhibition of fungal dihydroorotate dehydrogenase (DHODH) leading to disruption of DNA synthesis	*Aspergillus*, *Scedosporium*, *Lomentospora*, *Coccidioides immitis*, *Histoplasma capsulatum*
Opelconazole	Inhibition of ergosterol synthesis by blocking the enzyme lanosterol 14α demethylase	*Aspergillus*
Oteseconazole	Inhibition of ergosterol synthesis by blocking the enzyme lanosterol 14α demethylase	*Candida*
Rezafungin	Inhibition of β-(1,3)-D-glucan synthase, disruption of fungal cell wall formation	*Candida*, *Pneumocystis*, combination therapy against *Aspergillus*

as a promising first-in-class antifungal candidate. Further research will determine its clinical efficacy and role in therapy, potentially making NP339 a valuable addition to the limited arsenal of antifungal therapies currently available.[27]

These approved drugs, along with the promising candidates in clinical development, contribute to improving the management of fungal infections by offering diverse mechanisms of action, routes of administration, and potentially enhanced efficacy (Table 1). Continued research and development in this field are essential to address the challenges posed by fungal infections, especially considering the emergence of drug-resistant strains.

Antifungal drugs in the context of low- and middle-income countries

It is estimated that more than 6.5 million people each year suffer from invasive fungal infections and chronic pulmonary aspergillosis.[23] Some fungal infections are globally significant, with modest regional variations, while others are specific to certain geographic areas. Some LMICs exhibit demographic and socioeconomic factors that elevate the risk of fungal infections.[23,97,98] In 2022, the World Health Organization (WHO) published its first fungal priority pathogens list, highlighting that most of these pathogens are highly prevalent in LMIC.[126] While candidiasis and aspergillosis remain prevalent worldwide, certain LMICs also experience a significant number of cases of other opportunistic mycoses such as mucormycosis and fusariosis, HIV-related mycoses like cryptococcosis and pneumocystosis, as well as endemic mycoses including paracoccidioidomycosis, coccidioidomycosis, histoplasmosis, sporotrichosis, and talaromycosis.[23,85,95,104]

The incidence of fungal infections continues to rise, particularly in immunocompromised individuals. However, treatment options and the availability of antifungal drugs are limited and often associated with high costs, potentially harmful side effects and drug-drug interactions.[80] The antifungal drugs used listed on the WHO's Essential Medicines List include fluconazole, itraconazole, voriconazole, amphotericin B (as sodium deoxycholate or liposomal complex), flucytosine and echinocandins (micafungin, caspofungin, anidulafungin). Nystatin, griseofulvin and clotrimazole are also listed, although they are not generally used for systemic infections.[127] In terms of availability and accessibility of antifungal drugs in LMICs, azoles such as fluconazole and itraconazole, along with amphotericin B deoxycholate, are the most widely used. Fluconazole is considered the most widely available antifungal drug and is still employed in the treatment of candidemia or invasive candidiasis, mucosal and superficial candidosis, and the consolidation and maintenance phases of cryptococcal meningitis treatment. In many countries, it is provided free of charge because governments have included it in their lists of essential medicines.[11,68] Another antifungal from the triazole group that is commonly used in LMICs, although its distribution is lower compared to fluconazole, is itraconazole. This drug is generally used for the treatment of endemic mycoses, but it is only freely accessible in a few countries, such as Brazil, and sometimes only in specific locations within these countries. This poses a significant public health challenge because some endemic mycoses, such as paracoccidioidomycosis, chromoblastomycosis, and sporotrichosis, require prolonged treatment. These conditions frequently impact patients residing in rural areas with restricted economic resources, requiring extensive travel to acquire necessary medication.[11,68,79,84] Despite this, the consumption of antifungal drugs in LMIC has increased in recent years, with itraconazole being the most commonly used.[93] Voriconazole, the drug most used for treating invasive aspergillosis, has low availability in LMICs. It is available in about 30% of some African countries, and although in some Latin American countries the availability is higher, the acquisition costs are substantial. Echinocandins, the treatment of choice for candidemia, and newer azoles such as posaconazole and isavuconazole, are even less available.[11,16,92,98] Amphotericin B is highly available as amphotericin B deoxycholate. Despite its toxicity,[111] it continues to be used for treating some opportunistic mycoses, such as cryptococcosis and mucormycosis. About 90% of Latin American countries and nearly 50% of countries in Africa and Asia have access to this drug, while the availability and accessibility of its liposomal form are much lower in LMICs (Fig. 1).[16,25,68,98]

Flucytosine, mainly used for treating cryptococcosis, is the least available antifungal drug in LMICs and also faces limitations in non-LMICs.[30] Lack of data and awareness on fungal infections are obstacles to the availability of antifungal drugs in LMIC. Few cases of fungal infections are routinely diagnosed or reported by physicians and researchers, leading to fungal diseases and antifungal drugs being neglected in public health policies in many LMICs.[21,25,80] This situation severely compromises the treatment of certain fungal infections like mucormycosis and cryptococcosis in countries without amphotericin B, candidemia by fluconazole-resistant *Candida* in countries without echinocandins, and the treatment of invasive aspergillosis or lomentosporiosis in the absence of voriconazole.[11]

The use of antifungal drugs as prophylaxis in LMICs for patients with risk factors for invasive fungal infections is directly related to their availability. Fluconazole is almost the only drug used, pri-

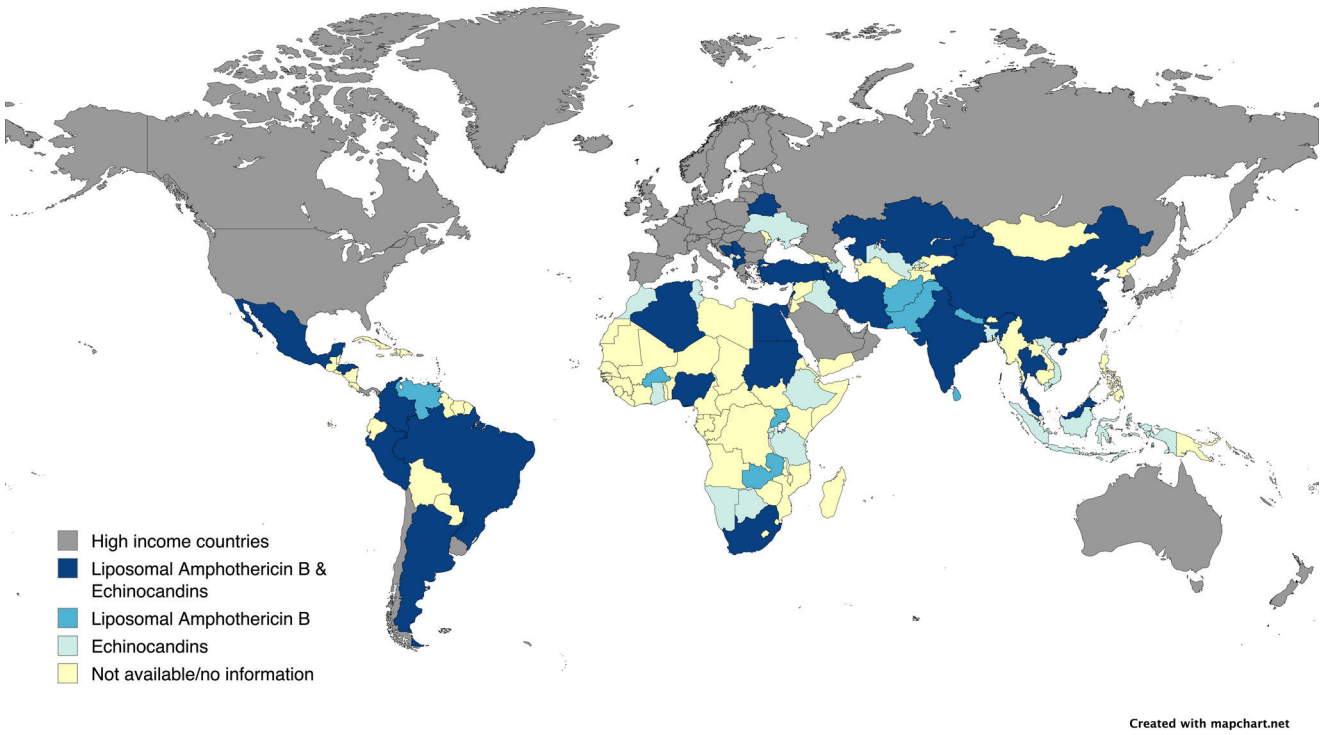

Fig. 1. Global availability of liposomal amphotericin B and echinocandins (caspofungin, micafungin and andulafungin) in low- and middle-income countries. Created with mapchart.net.

marily to prevent invasive candidiasis, while other drugs such as voriconazole or posaconazole are used as prophylaxis in very few countries to prevent invasive infections by filamentous fungi.[85,98]

Maps showing the availability of azoles, echinocandins and liposomal amphotericin B in LMICs are illustrated in Figs. 1 and 2. LMICs were selected based on economic data provided by the World Bank and defined by gross national income per capita as follows: Low-income countries ($1085 or less), lower-middle income countries ($1086–$ 4255) upper-middle income countries ($ 4256–$13,205).[117] Data for Africa were adapted from Bongomin et al.,[11] while data for Asia, Pacific and Europe were provided by Jon Salmanton-García and Global Actions For Fungal Infections (GAFFI).[38] A detailed table showing drug availability for each country is available in the supplementary files.

Another important aspect in the scenario of antifungal drugs in LMICs is access to therapeutic drug monitoring, which plays a crucial role in optimizing drug dosages, managing toxicity, and promoting the appropriate use of medications. Falci and Pasqualotto[30] reported that in Latin America, access to therapeutic drug monitoring is scarce; voriconazole was the drug most frequently measured (16%), followed by itraconazole (10%) and posaconazole (4%), with most serum drug measurements being made in outsourced laboratories (79%). In a study conducted in African countries, Driemeyer and colleagues[25] reported that therapeutic drug monitoring was available for itraconazole in seven (17,5%) institutions in-house and in two (5%) institutions at outsourced laboratories. Regarding therapeutic drug monitoring for other antifungal agents, voriconazole was available in four (10%) institutions, posaconazole in one (2.5%) institution, and 5-flucytosine in three (7.5%) centers in total, both in-house and outsourced. The limited availability of therapeutic drug monitoring is concerning as it plays a critical role in determining the appropriate usage of essential medications like voriconazole and itraconazole.[25]

Prescription of antifungal drugs poses a real challenge in LMIC as antifungal stewardship is not adopted in most of these countries. Incorrect prescriptions and inappropriate use of antifungal drugs can lead to the development of antifungal resistance, a growing global public health issue in LMICs with limited available data.[46,98] This includes, for example, the antifungal drug not being selected on the basis of laboratory results, being administered in an inappropriate dose and not for the required duration.[98] Inappropriate use of antifungal treatments by patients, who usually do not complete their treatment, is also a major reason for the development of resistance in LMICs.[80] Additionally, poor practices like self-prescription at inappropriate doses and purchasing antifungals on the black market (sometimes expired) pose significant threats to individual health (due to drug intoxication) and public health in general (due to the development of antifungal resistance).[25,46]

Conclusion and future directions

The increasing incidence of fungal infections and new fungal pathogens, such as *C. auris*, in combination with antifungal resistance, is a major challenge for global public health. Current treatment options are limited and often associated with adverse effects and declining efficacy due to resistance. New antifungal drugs such as ibrexafungerp, rezafungin, oteseconazole and miltefosine provide hope as they offer new mechanisms of action, new modes of administration and the potential for improved safety and efficacy. In addition to the development of new antifungal drugs, alternative strategies such as combination therapies (using antifungal drugs together with other agents), immunomodulation[1] and vaccines are being actively developed for the treatment of fungal infections.[75] Although protection against all major medical mycoses has been achieved in animal models with a variety of vaccine designs ranging from subunit formulations to live attenuated fungi,[87] there are currently no fungal vaccines licensed for use in humans.[61] In addition, novel natural compounds such as peptides, lipopeptides and retinoids have shown potential efficacy in inhibiting *Candida* growth, although these results are still preliminary and further investigation in clinical trials is required.[35]

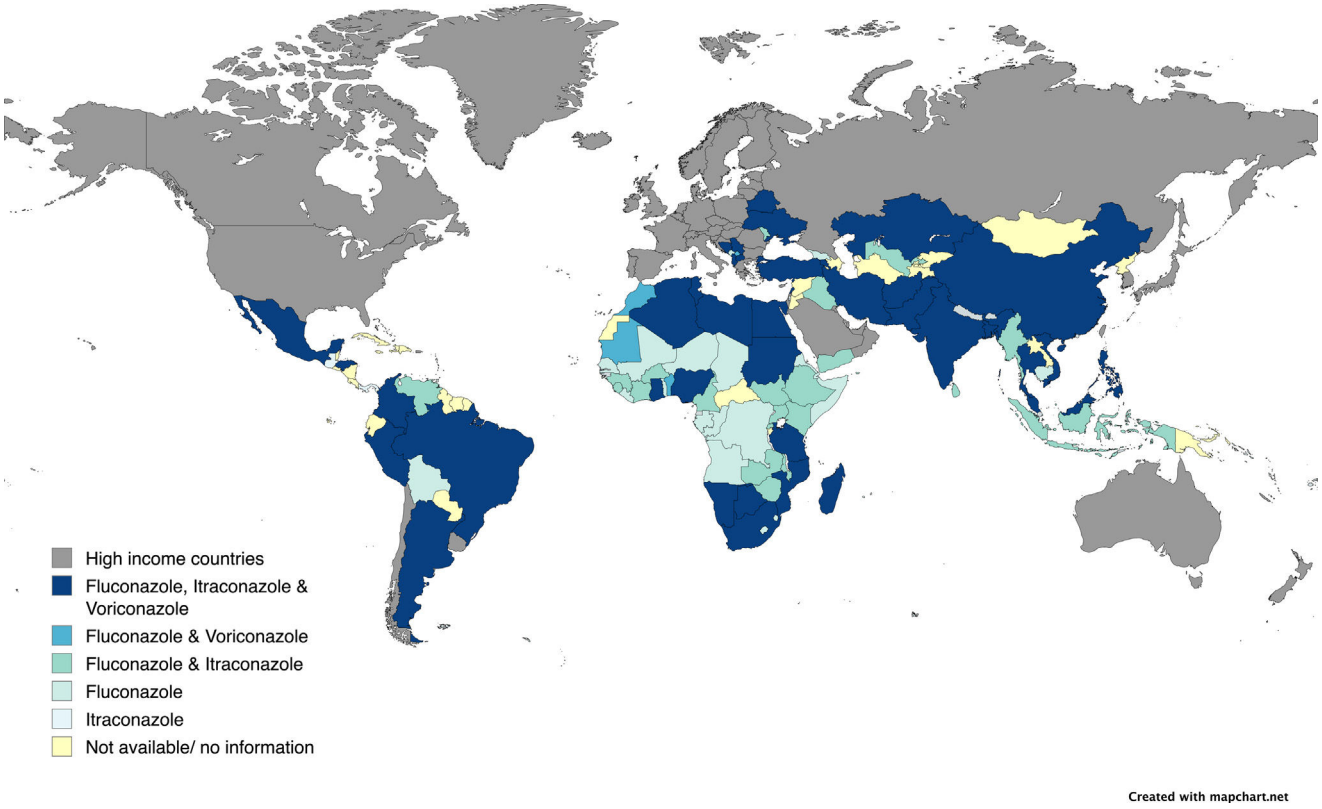

Fig. 2. Global availability of azoles in low- and middle-income countries. Created with mapchart.net.

However, the accessibility and affordability of these new treatments, particularly in LMICs, remains a major obstacle. In LMICs, the availability and cost of effective antifungal treatments pose challenges for proper management of fungal infections. Further complicating matters are the absence of adequate therapeutic monitoring and prescribing practices, leading to a heightened risk of antifungal resistance. It is imperative to establish public health policies that target these shortcomings in order to enhance outcomes in LMICs. Antifungal targets play a crucial role in treating fungal infections, especially in immunocompromised patients where these infections can be life-threatening and may provide new solutions to overcome the limitations of currently available antifungal drugs and address the issue of resistances.[10,71,132]

Authorship

SW contributed to drafting and writing of the manuscript and designed the figures. JSG provided data for the maps, contributed to writing and proof-reading. MPNK, MH and JGPB contributed to writing and proof-reading of the manuscript. All authors have read and approved the manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used GPT-4 (OpenAI©) in order to improve readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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JSG has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Gilead, Menarini, and Pfizer; and has participated on a Data Safety Monitoring Board or Advisory Board for Pfizer, outside of the submitted work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.riam.2024.11.001.

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