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AN OVERVIEW OF AZOLE ANTIFUNGALS

Pratibha Shivaji Gavarkar*, Rahul Shivaji Adnaik, and Shrinivas Krishna Mohite

Rajararambapu College of Pharmacy, Kasegaon, Tal. Walwa, Dist. Sangli- 415404, Maharashtra, India

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Correspondence to Author:

Smt. Pratibha Shivaji Gavarkar

Assistant Professor, Department of Pharmaceutical Chemistry, Rajararambapu College of Pharmacy, Kasegaon, Tal. Walwa, Dist. Sangli 415404, Maharashtra, India

E-mail: pratibhagavarkar@gmail.com

ABSTRACT: Fungal infections in critically ill or immunosuppressed patients were increasing in incidence in the human population over the last 1-2 decades. There were few advances in antifungal therapy and, until recently, there were few choices from which to select a treatment for systemic mycoses. However, in the past decade, there have been several developments in this area. Antifungal agents are sufficiently diverse in activity, toxicity, and drug interaction potential. Azoles are synthetic and semi-synthetic compounds. They have a broad spectrum of activity. Triazole antifungals are active to treat an array of fungal pathogens, whereas imidazoles are used almost exclusively in the treatment of superficial mycoses and vaginal candidiasis. Despite the advances, serious fungal infections remain difficult to treat, and resistance to the available drugs is emerging. Use of the currently available azoles in combination with other antifungal agents with different mechanisms of action is likely to provide enhanced efficacy. The present review aims to explore the pharmacology, pharmacokinetics, spectrum of activity, safety, toxicity and potential for drug–drug interactions of the azole antifungal agents.

INTRODUCTION: Fungi are common pathogens in critically ill or immunosuppressed patients. Fungal infections (mycoses), though not as frequent as bacterial or viral infections, have nonetheless been increasing in incidence in the human population over the last 1-2 decades. In addition, a number of fungal infections can be difficult to treat, even when the offending organism is identified and appropriate therapy is applied. Fungi have unique characteristics, distinct from their mammalian hosts, allowing for selective targeting of therapeutic drugs.

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Fungi are, however, much more complex organisms in comparison to bacteria, are in fact eukaryotic and often grow fairly slowly. Consequently, only a few drugs are aimed at interfering with cell division and have limited use.

However, in the past decade, there have been several developments in advances in antifungal therapy to select a treatment for systemic mycoses. A new class of antifungal agents (echinocandins) has been developed, safer and/or more bioavailable formulations of itraconazole and amphotericin B have been marketed, and another compound-voriconazole has been added to the triazole class of agents. Antifungal agents are sufficiently diverse in activity, toxicity, and drug interaction potential to allow clinicians to differentiate among agents based upon these characteristics when tailoring therapy to meet the needs of a particular patient.

The present review focuses on the pharmacology, pharmacokinetics, safety, and potential for drug-drug interactions of the antifungal agents [1-4].

Azoles are synthetic and semi-synthetic compounds as shown in **Table 1**. They have a broad spectrum of activity.

TABLE 1: CLASSIFICATION OF ANTI-FUNGAL AGENTS

Class	Route of administration	Examples
Imidazole group	Topical agents Systemic agent	Clotrimazole, Econazole miconazole, butaconazole, Ketoconazole
Triazole group	Topical agent Systemic agents	teraconazole, itraconazole, fluconazole, itraconazole, voriconazole

Pharmacology of Azoles:

Mechanisms of Action: The systemically acting azoles include fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole. The azoles exert a fungistatic effect by dose-dependent inhibition of CYP-dependent 14α-demethylase, which is necessary for the conversion of lanosterol to ergosterol.Ergosterol is important for the stability of the fungal cell membrane, and inhibition of its synthesis compromises cell membrane integrity [2].

The triazoles also secondarily target other steps in the ergosterol biosynthesis pathway.

For example, in fluconazole-susceptible *C. albicans* fluconazole only partially inhibits ergosterol and completely blocks obtusifoliol synthesis, whereas voriconazole completely inhibits both ergosterol and obtusifoliol synthesis [5]. Itraconazole and fluconazole may also inhibit 3-ketoreductase, which catalyzes the reduction of the 3-ketosteroid obtusifolione to obtusifoliol in *C. neoformans* [6].

All azoles act much more slowly than polyenes. Thus they are used less often than polyenes in treatment of fulminating fungal infections. Some of the important azoles along with their indications, brand name and available formulation are listed in the **Table 2**.

TABLE 2: AZOLES AS ANTIFUNGAL AGENTS

Agent	Indications	Brand Name	Available formulation
Fluconazole	Vaginal, oropharyngeal, and esophageal candidiasis; cryptococcal meningitis; prophylaxis to decrease the incidence of candidiasis in patients undergoing BMT who receive cytotoxic chemotherapy and/or radiation.	Diflucan (Pfizer)	IV, oral suspension, oral tablet
Itraconazole	**I.V., oral capsule:** Pulmonary and extrapulmonary blastomycosis; histoplasmosis, including chronic cavitary pulmonary disease and disseminated, nonmeningeal histoplasmosis; aspergillosis in patients who are refractory to or intolerant of amphotericin B therapy. **Oral capsules only:** Non-immunocompromised patients: treatment of onychomycosis of the toenail, with or without fingernail involvement, or of the fingernail alone, due to dermatophytes (tinea unguium). **I.V., oral solution only:** Empiric therapy of febrile neutropenic patients with suspected fungal infections. **Oral solution only:** Oropharyngeal and esophageal candidiasis.	Sporanox, (Janssen/ Ortho-McNeil)	IV, oral capsule, oral solution
Ketoconazole	Candidiasis, chronic mucocutaneous candidiasis, oral thrush, candiduria, blastomycosis, coccidioidomycosis, histoplasmosis, chromoblastomycosis, and paracoccidioidomycosis; severe recalcitrant cutaneous dermatophyte infections that have not responded to topical therapy or oral griseofulvin, or in patients unable to take griseofulvin.	Nizoral (Janssen/ Ortho-McNeil; various)	Oral tablet
Voriconazole	Invasive aspergillosis; candidemia in nonneutropenic patients and the following Candida infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds;	Vfend, (Pfizer)	IV, oral tablet

	esophageal candidiasis; serious fungal infections caused by Scedosporium apiospermum (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp, including *F. solani*, in patients intolerant of, or refractory to, other therapy.

Spectrum of Activity: Azoles possess broad spectrum of activity against yeasts and moulds. However, as this therapeutic class expands, differences in spectrum of activity among the individual agents emerge. The difference in spectrum of activity exhibited among different azoles may be attributed to variation in the inhibition of 14α-demethylase and secondary targets among species. **Table 3** shows spectrum of activity of various azoles.

TABLE 3: SPECTRUM OF ACTIVITY OF AZOLES

Agent	Spectrum of activity
Fluconazole [6-9]	• *In-vitro* activity of fluconazole is generally considered fungistatic • Relatively narrow spectrum of activity is limited to yeasts • Very active against *Candida* species including *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. lusitaniae and m*uch less active against other *Candida* spp. • *C. krusei* is inherently resistant, and species such as *C. glabrata* and C. *guilliermondii* have reduced susceptibilities to fluconazole • Fluconazole also has activity against *C. neoformans* and *Coccidioides immitis* • Fluconazole has no activity against *Aspergillus* spp., *Fusarium* spp. and the agents of zygomycosis.
Itraconazole [10-12]	• Fungicidal activity against filamentous fungi and some strains of *C. Neoformans* and is generally fungistatic against many yeasts • Moderately to very active against most medically important fluconazole-susceptible and -resistant *Candida* species (except *C. Glabrata)* • Modest activity against *C. Neoformans* • Excellent in vitro activity against common dimorphic or endemic fungi including *C. Immitis*, *H. capsulatum*, *B. Dermatitidis*, and *S. Schenckii*. • Good activity against many *Aspergillus* spp. But it has variable activity against *Fusarium* spp. And very limited activity against the agents of zygomycosis
Voriconazole [6-9, 11]	• Fungicidal activity against most yeasts and certain opportunistic fungi, and fungicidal activity against some non-*albicans Candida* spp. And *C. neoformans.* • Very broad spectrumof activity against dermatophytes, yeasts, and moulds. • Active against all *Candida* spp., including fluconazole-resistant *C. Albicans*, *C. Glabrata*, and *C. Krusei* • More active than fluconazole against medically important *Candida* spp. (excep *C. Tropicalis)* • Very active against other yeasts, including *C. Neoformans* and most *Trichosporon* spp., including *T. Asahii*, but it is not very active against *T. Beigelii*/*T. Cutaneum* • Excellent in vitro activity against *Aspergillus* spp. And is highly active against *A. Fumigatus*, *A. Flavus*, and *A. Terreus.* • Active against many amphotericin-resistant moulds, including certain strains of *Scedosporium apiospermum* • Similar to fluconazole, voriconazole has poor or no activity against the agents of zygomycosis.
Posaconazole [13-16]	• Fungicidal activity against non-*albicans Candida* species including *C. Krusei*, *C. Inconspicua* and *C. Lusitaniae*, but is fungistatic against *C. Albicans*, *C. Glabrata*, *C. Tropicalis*, *C. Guilliermondii* and *C. Parapsilosis*. • Like voriconazole, posaconazole demonstrates in vitro fungicidal activity against *Aspergillus* spp and *C. Neoformans*. • More active than itraconazole and fluconazole against all *Candida* spp. And *C. Neoformans*. • In vitro, posaconazole is the most active azole against *Aspergillus* spp. And is highly active against *A. Fumigatus*, *A. flavus*, and *A. Terreus*. • Very potent activity against the dimorphic fungi including *C. Immitis*, *H. Capsulatum*, *B. Dermatitidis*, and *S. Schenckii*. • Variable activity against many amphotericin-resistant molds, including certain strains of *Scedosporiumapiospermum* and *P. Boydii*, but is not active against *Fusarium* spp. • Variable activity against the agents of zygomycosis.

Pharmacokinetics of Azoles: Chemically, azoles are lipophilic weak bases. All azoles have good relative or absolute bioavailability after oral administration (except the capsule form of itraconazole). Dissolution of ketoconazole and itraconazole in the stomach, administered as solid oral dosage forms are significantly influenced by elevations in gastric pH [17, 18]. Azoles (except posaconazole) require extensive oxidative (CYP) metabolism to be eliminated from the body [19, 20]. Unlike the other triazoles, posaconazole undergoes minimal (2%) CYP metabolism; most of its metabolites are glucuronide conjugates formed by uridine diphosphate glucuronosyltransferase (UGT) pathways, mainly UGT1A4 [21, 22].

Fluconazole is less lipophilic, and therefore it requires less oxidative (CYP) metabolism. The azoles are inhibitors of CYP3A4, the primary oxidative drug-metabolizing enzyme in humans [23, 24]. However, the azoles all differ in their affinity for this enzyme. Fluconazole and voriconazole also inhibit CYP2C9/19, and fluconazole inhibits a UGT pathway (UGT2B7) [23, 25]. The significance of the interaction is unknown.

Drug disposition is facilitated by a variety of transport proteins which are expressed in tissues throughout the body in humans. Azoles and echinocandins vary in their interactions with transport proteins [26-28].

Itraconazole, ketoconazole, and posaconazole interact with P-glycoprotein, the best-known efflux transport protein.[28] Ketoconazole and itraconazole interact with another transporter, known as breast cancer resistance protein (BCRP) [28]. The significance of these interactions with BCRP have not been fully elucidated, but they may, in part, explain certain interactions that previously could not be adequately described by interactions with CYP.

Toxicity of Azoles [29-32]: The primary toxicities associated with the azoles involve the liver have been shown in the **Table 4** and **Table 5**. These toxicities range from the common transient elevations in serum transaminases to the less common fulminant hepatoxicity and liver failure. Liver failure is rare but it may occur with any azole.

TABLE 4: TOXICITY OF AZOLES

Agent	Toxic effect
Voriconazole	• Produces clinically significant transaminase abnormalities in approximately 13% of patients. • Produces visual disturbances in approximately 20% to 30% of subjects in clinical trials.
Itraconazole	• Has been associated with the development of congestive heart failure. In such case risk and benefits of using itraconazole for non–life-threatening infections (eg, onchyomycosis) must be seriously considered.
Ketoconazole	• produce endocrine abnormalities that lead to gynecomastia and adrenocortical insufficiency (because of its lack of selectivity for fungal CYP)

The underlying mechanism of above side effect has not been elucidated, but it is believed to be concentration- or dose-related.

TABLE 5: ADVERSE EFFECTS OF AZOLES

Agent	Adverse Effects
Fluconazole	• **Cardiopulmonary:** Hypotension (rare), peripheral/pulmonary edema (rare) • **CNS:** Dizziness (rare), headache, seizure (rare) • **Dermatologic/Hypersensitivity:** Anaphylaxis, eosinophilia, pruritus, rash • **Electrolyte Disturbances:** Hypokalemia (rare) • **Gastrointestinal:** Abdominal pain/dyspepsia, diarrhea, dysgeusia, nausea/vomiting • **Hematologic:** Anemia (rare), myelosuppression (rare), thrombocytopenia (rare) • **Hepatic:** LFT; hepatic necrosis/hepatitis/cholestasis • **Miscellaneous:** Alopecia, fever (rare)
Itraconazole	• **Cardiopulmonary:** Congestive heart failure, hypertension (rare), peripheral/pulmonary edema, tachycardia (rare), tachypnea (rare) • **CNS:** Dizziness (rare), headache • **Dermatologic/Hypersensitivity:** Anaphylaxis, eosinophilia, pruritus, rash

	• **Electrolyte Disturbances:** Hypokalemia (rare) • **Endocrine**: Altered hormone levels (rare), gynecomastia (rare) • **Gastrointestinal:** Abdominal pain/dyspepsia, diarrhea, flatulence (rare), nausea/vomiting • **Hepatic:** LFT, hepatic necrosis/hepatitis/cholestasis • **Miscellaneous:** Fever (rare), alopecia (rare)
Ketoconazole	• **Cardiopulmonary:** Hypertension (rare) • **CNS:** Headache • **Dermatologic/Hypersensitivity:** Anaphylaxis, eosinophilia, pruritus, rash • **Endocrine:** Adrenocortical insufficiency, altered hormone levels, gynecomastia, inhibition of cortisol synthesis • **Gastrointestinal:** Abdominal pain/dyspepsia, diarrhea, flatulence (rare), nausea/vomiting; • **Hematologic:** Anemia (rare), myelosuppression (rare), thrombocytopenia • **Hepatic:** LFT, hepatic necrosis/hepatitis/cholestasis • **Miscellaneous:** Fever (rare)
Voriconazole	• **Acute Infusion Reactions**: Fever (rare), nausea/vomiting (rare), visual disturbances • **Cardiopulmonary:** Congestive heart failure (rare), hypertension (rare), hypotension (rare), peripheral/pulmonary edema (rare), tachycardia (rare) • **CNS:** Dizziness (rare), hallucinations (rare), headache, seizure (rare) • **Dermatologic/Hypersensitivity:** Anaphylaxis, eosinophilia, pruritus, rash • **Electrolyte Disturbances** Hypokalemia (rare) • **Endocrine:** Adrenocortical insufficiency (rare), altered hormone levels (unknown), gynecomastia (unknown), inhibition of cortisol synthesis (unknown) • **Gastrointestinal:** Abdominal pain/dyspepsia, diarrhea, dysgeusia (unknown), flatulence (rare), nausea/vomiting • **Hematologic:** Anemia (unknown), myelosuppression (unknown), thrombocytopenia (unknown) • **Hepatic:** LFT, hepatic necrosis/hepatitis/cholestasis • **Miscellaneous:** Alopecia (unknown), fever (unknown), joint/muscle pain (rare)

Drug-Drug interactions of Azoles: Drug interactions associated with the azoles result from several different mechanisms. These agents can interact with drugs through different mechanisms (e.g. pharmacodynamic, pH, complexation and electrostatic interactions, CYP and P-glycoprotein). Interactions involving the azoles are pharmaco-kinetic and result as a consequence of their physicochemical roperties [33-35]. Ketoconazole and itraconazole are subject to pH-based and metabolic interactions.

Drugs that will likely interact with these azoles include agents that are cationic or increase gastric pH or are lipophilic CYP3A4 substrates with poor oral availability. All azoles are weak bases and at elevated pH values, weakly basic compounds dissolve more slowly.

Therefore, the absorption of azoles such as the capsule form of itraconazole is influenced by alterations in gastric pH. Many of the azoles are lipophilic and thus they are subjected to interactions involving their biotransformation and disposition. Fluconazole is hydrophilic and is highly soluble in water and therefore, compared to the other azoles, it requires much less biotransformation to be eliminated from the body [36-37]. Itraconazole, voriconazole, and posaconazole are highly lipophilic and have limited aqueous solubility. Therefore, these azoles must undergo extensive enzymatic conversion to more polar metabolites in order to be eliminated from the body.

Resistance of Azoles: Since the advances in development of the azole group of antifungal compound for the treatment of fungal infections, it has got widespread use. Consequently, with extensive use resistance to these agents has been reported, particularly fluconazole. [38-41] Azole resistance in *Candida* has been the most widely observed and studied for fluconazole Resistance to the azoles is attributed to quantitative or qualitative modifications of target enzymes, reduced access of the drug to the target enzyme or by a combination of these mechanisms.

Qualitative modifications in target enzymes result from point mutations in *ERG11*, the gene responsible for producing 14α-demethylase, which is the principal target of the azoles.

Alternatively, the different chemical structures of the azoles may also contribute to this differential activity. Quantitative modifications in target enzymes also result from mutations in *ERG11*. Overexpression of the gene results in over-production of the target enzymes, which then necessitates higher intracellular azole concentrations to inhibit all the target enzyme.[42-43]

CONCLUSION: The incidence of infection with invasive mycoses continues to increase with the increasing immunosuppressed patients. The therapy of fungal infections has undergone an explosive period of development in recent years. The azole group of compounds has provided excellent therapy in the treatment of most clinically important mycoses. Clinicians must recognize the differences in toxicity and potential for drug–drug interactions to use these agents optimally. Further advances in antifungal chemotherapy will be necessary to improve management of invasive mycoses in the future.

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