Correspondence

Drug Repurposing Identifies New Promising Treatment Options for Invasive Fungal Diseases

The resistance of microorganisms to antimicrobial agents threatens the efficacy of drugs available for their treatment. This threat is worrisome with regard to fungal pathogens involved in aggressive invasive infections because there are low numbers of antifungals available and their resistance is increasing.[1]

Currently, only 3 major classes of antifungal drugs are available. The occurrence of resistance and multidrug resistance results in difficulties in patient treatment. One of the larger challenges encountered is resistance to azoles by the genera *Candida* and *Aspergillus* in which dissemination of resistant strains of *Aspergillus fumigatus* and recently multidrug-resistant *Candida auris* is considered an emerging threat. *C auris* is involved in numerous outbreaks worldwide, with a mortality rate close to 60%. Consequently, resistance to echinocandins by some species of *Candida*, mainly *glabrata*, also occurs[2,3] Thus, there is an urgent need to increase the number of therapeutic options available for the treatment of fungal infections, leading researchers to search for alternatives.

Drug repositioning, also known as redirecting, repurposing, and reprofiling, has emerged as an effective possibility in the discovery of treatments against fungal infections.[4] This process is defined as a new application of an existing or failed drug in addition to its original indication. Drug repositioning is identified as a rapid identification of new therapeutic agents because pharmacodynamic and pharmacokinetic data and levels of toxicity are available.[5] In Table I, we present a selection of studies that investigated the antifungal activity of several pharmacologic classes as alternatives in repositioning, among them, statins, antivirals, and antidepressants. To obtain this information, we conducted a search in 3 databases (PubMed, SCOPUS, and Web of Science). The databases were searched from April 5 to May 5, 2019, using the following search strategy: [(repositioning) AND (repurposing) AND (redirecting) AND (reprofiling) AND (rediscovery)], with revision filters appropriate for individual databases. Inclusion criteria were studies that contemplated the repositioning of drugs with antifungal activity. In duplicate cases, one study was excluded. Also excluded were those studies that did not address the topic in the article content.

The present studies point to antifungal activities in *in vitro* and *in vivo* assays and, in some cases, elucidate the mechanism of action involved, such as the immunomodulation of calcitriol against *Candida albicans* and *Candida tropicalis*. Other evidence is the occurrence of a synergistic association between repositioning drugs and routinely used antifungals, such as in the interaction of simvastatin with itraconazole, fluconazole, and amphotericin B. This occurrence is relevant because combinations of 2 or more compounds that have different mechanisms of action can increase the success rate of repositioning.

After the analysis of several studies, we found that drug repositioning and its combination with usual antifungals are promising and innovative alternatives for the treatment of fungal infections, especially those caused by the genera *Candida*, *Cryptococcus,* and *Aspergillus*. This method may benefit patients through safer and more effective therapy compared with monotherapeutic regimens. In addition, extrapolating from antibiotic therapy of

Table I. Studies of the repositioning of nonantifungal drugs with antifungic effect.

Class	Drug	Original Indication	New Indication in Repositioning	Type of Study	Active Concentration MIC, μg/mL	Probable Mechanism of Action	Synergistic Effect	MIC Range for Antibiotics Alone Before Combination	MIC Range for Synergistic Association (Nonantibiotic or Antibiotic), μg/mL	Reference
Antiviral	Raltegravir	HIV-1 infection	*Paracoccidioides brasiliensis*	*In vitro* and	16	Not elucided	—	—	—	6
			Paracoccidioides lutzii	*in vivo*	32		—	—	—	
Selective Serotonin Reuptake inhibitor	Fluoxetine	Antidepressant	*Candida glabrata*	*In vitro*	—	Not elucided	—	—	—	7
			Candida parapsilosis (biofilm)	*In vitro*	—		—	—	—	
			Candida albicans	*In vitro*	156—625		Fluconazole	0.25—32	19—156/0.125—1	8
			C glabrata	*In vitro*	9.8—156		Fluconazole	4—32	4.9-39 /1—8	
			Candida guilliermondii	*In vitro*	39— 312.3		*	*	*	
			Candida krusei	*In vitro*	78— 312.3		Fluconazole	Resistant	9.8 /0.12—8	
			C parapsilosis	*In vitro*	156— 625		Fluconazole	64	9.8/4	
			Candida tropicalis	*In vitro*	156—312		Fluconazole	4-8	4.9—19/1—2	
			Candida phaerica	*In vitro*	9.8		*	*	—	
			Candida lipolytica	*In vitro*	156		*	*	—	
			C albicans	*In vitro*	40—100.8	Activates apoptotic signaling pathways and leads to dose-dependent cell viability loss	—	—	—	9
			C tropicalis	*In vitro*	40—160					
			C parapsilosis	*In vitro*	20—160					
			C glabrata	*In vitro*	80					
	Paroxetine	Antidepressant	*C albicans*	*In vitro*	63.5—80					9
			C tropicalis	*In vitro*	80— 100.8					
			C parapsilosis	*In vitro*	40—80					
			C glabrata	*In vitro*	63.5					
	Sertraline	Antidepressant	*C albicans*	*In vitro*	20					9
			C tropicalis	*In vitro*	20					
			C parapsilosis	*In vitro*	10-20					
			C glabrata	*In vitro*	15.9					
			C albicans	*In vitro*	32	Influence on membrane stability or vesicle transport in fungi	*	*	*	10
			C glabrata	*In vitro*	12		*	*	*	
			C krusei	*In vitro*	12		*	*	*	
			C parapsilosis	*In vitro*	24		*	*	*	
			C tropicalis	*In vitro*	24		*	*	*	
			Candida lusitaniae	*In vitro*	8		*	*	*	
			Cryptococcus species	*In vitro*	6-10		Fluconazole	6-64	1—6/2—32	
			Cryptococcus neoformans	*In vivo*	—		—	—	—	
			Cryptococcus spp	*In vitro*	1—8	Probably through perturbation of	—		—	11
			C neoformans	*In vivo*	15 mg/kg		—		—	

(*continued on next page*)

Table I. (*Continued*)

Class	Drug	Original Indication	New Indication in Repositioning	Type of Study	Active Concentration MIC, μg/mL	Probable Mechanism of Action	Synergistic Effect	MIC Range for Antibiotics Alone Before Combination	MIC Range for Synergistic Association (Nonantibiotic or Antibiotic), μg/mL	Reference
						translation protein synthesis				
			Treatment of *cryptococcal meningitis*	*In vivo*	1-8	Inhibits mRNA translation into protein synthesis	Fluconazole	†	†	12
			C albicans	*In vitro*	6.3—25	Mediated through a nonspecific mechanism related to the lipophilicity of theagents				13
			Saccharomyces cerevisiae	*In vitro*	6.3					
			C krusei	*In vitro*	6.3					
			C tropicalis	*In vitro*	12.5					
			C parapsilosis	*In vitro*	25					
			Aspergillus fumigatus	*In vitro*	25					
			C glabrata	*In vitro*	—	Not elucided				7
			C parapsilosis (biofilm)	*In vitro*	—					
			Trichosporon asahii	*In vitro*	4—8		Amphotericin B, caspofungin and fluconazole	0.25—4 8—32 1—16	0.5—2/0.03—0.125 0.5—4/0.5—8 1—4/0.25—1	14
			C neoformans	*In vitro*	10.8—43		Fluconazole	4.1—17.8	2.5—4.3/1.7—3.4	15
			C gattii	*In vitro*	10.8—43		*		*	
			Aspergillus niger	*In vitro*	20—80		—		—	16
			A fumigatus	*In vitro*	80—100					
			Aspergillus flavus	*In vitro*	60-80					
			Fusarium solani	*In vitro*	80					
			C albicans	*In vitro*	3—29		—		—	16
			C glabrata	*In vitro*	14—29					
			C tropicalis	*In vitro*	3—7					
			C parapsilosis	*In vitro*	14—29					
Statin	Atorvastatin	Hypercholesterolemia	*C gattii*	*In vitro and in vivo*	256	Alteration of the polysaccharide capsule and fungal cell membrane	Fluconazole	2—16	†	17
			C albicans		16—32			†	†	18

Table I. (*Continued*)

Class	Drug	Original Indication	New Indication in Repositioning	Type of Study	Active Concentration MIC, μg/mL	Probable Mechanism of Action	Synergistic Effect	MIC Range for Antibiotics Alone Before Combination	MIC Range for Synergistic Association (Nonantibiotic or Antibiotic), μg/mL	Reference
			C glabrata	*In vitro and in vivo*	32	Stimulate farnesol-dependent pathogenic factors, such as yeast-to-hyphal transition and biofilm generation	Itraconazole, ketoconazole and fluconazole	† †	† †	
			C albicans	*In vitro*	52.06	Probable interference with ergosterol biosynthesis	—			19
	Simvastatin	Hypercholesterolemia	*C albicans*	*In vitro*	29.45		Itraconazole, fluconazole and amphotericin B	0.05–15.2	1–116.6/0.01–0.3	19
			C tropicalis	*In vitro*	70.12			0.8–82.3	1.6–49.5/0.1–4.8	
			C krusei	*In vitro*	567.16					
			C parapsilosis	*In vitro*	235.97			0.616–1.6	19–35.4/0.031	
			C neoformans	*In vitro*	62.5–500					
			C gatti	*In vitro*	500					
	Fluvastatin	Hypercholesterolemia	*C albicans*	*In vitro and In vivo*	1–8	Stimulate farnesol-dependent pathogenic factors, such as yeast-to-hyphal transition	Itraconazole, ketoconazole and fluconazole	† † †	† † †	18
			C glabrata	*In vitro*	32					
	Rosuvastatin	Hypercholesterolemia	*C albicans*	*In vitro*	8–128		Ketoconazole and fluconazole	† †	† †	18
			C glabrata		64					
Phenothiazine	Chlorpromazine	Antipsychotic	*C neoformans*	*In vitro*	1–32	Not elucided	Sertraline and amphotericin B	8–64 0.06–0.5	† †	20
Proton pump inhibitor	Esomeprazole	Gastritis	*C neoformans*	*In vitro*	125–500	Not elucidated	—	—	—	21
			C gatti	*In vitro*	125–500					
	Lanzoprazole	Gastritis	*C neoformans*	*In vitro*	125–1000		—	—	—	21
			C gatti	*In vitro*	125–1000					
	Omeprazole	Gastritis	*C neoformans*	*In vitro*	125–250		—	—	—	21
			C gatti	*In vitro*	125–250					
	Pantoprazole	Gastritis	*C neoformans*	*In vitro*	500–1000		—	—	—	21
			C gatti	*In vitro*	500–1000					
	Rabeprazole	Gastritis	*C neoformans*	*In vitro*	125–250		—	—	—	21
			C gatti	*In vitro*	125–250					
Vitamin	Calcitriol	Osteoporosis	*C albicans*	*In vitro*	0.5	Immunomodulatory role	—	—	—	22
			C tropicalis	*In vitro*	0.5		—	—	—	
4-Aminoquinoline	Chloroquine	Antimalarial	*C albicans*	*In vitro*	1000	Not elucided	—	—	—	23

* Other type of interaction.
† MIC value not sown (fractional inhibitory oncentration index value only).

bacteria, the combination of drugs does not generate resistance acquisition. However, additional studies on the mechanism of antifungal action of these drugs are still necessary to determine safe use of these agents in clinical practice.

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