Oral Terbinafine-, Fluconazole-, Ravuconazole-, Oteseconazole-induced Hepatotoxicity and Acute Kidney Injury in the Treatment of Onychomycosis: A Pharmacovigilance Study

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

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Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

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Approval

The thesis/project titled “Oral Terbinafine-, Fluconazole-, Ravuconazole-, Oteseconazole-induced Hepatotoxicity and Acute Kidney Injury in the Treatment of Onychomycosis: A Pharmacovigilance Study” submitted by Towsifur Rahman 19146076 of Spring, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on March 09, 2023.

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Ethics Statement

The project does not involve any clinical trial or human participants, no animals were used or harmed.

Abstract

Onychomycosis is a fungal infection in the nails. Oral antifungal therapies of onychomycosis; terbinafine, fluconazole, ravuconazole, otesaconazole may cause liver and acute kidney injury (AKI). This project aims to identify the signals of hepatotoxicity and AKI of these antifungals in the FDA Adverse Event Report System (FAERS) database.

We included FAERS records, calculating reporting odds ratios (RORs), and associated 95% confidence interval (CI). Statistical significance was considered when the lower limit of 95% CI exceeded 1.0. Isoniazid and gentamicin were added as controls for the adverse events.

Terbinafine's ROR (95% CI) was 5.20 (2.70, 10.01), and fluconazole's was 1.15 (0.58, 2.31) in hepatotoxicity. No signal was detected for AKI for these two antifungals. Isoniazid showed 3.32, and 15.01 times more hepatotoxicity; gentamicin showed 4.06, and 5.24 times more AKI-causing than terbinafine and fluconazole respectively. No clinical data for ravuconazole and otesaconazole was found.

The study supported the association between terbinafine and hepatotoxicity. It found no association between the drugs causing AKI.

Keywords: Antifungal-Induced Hepatotoxicity and Acute Kidney Injury; FDA Adverse Event Reporting System; Oral Terbinafine; Fluconazole; Ravuconazole; Oteseconazole.

Dedication

This work is the result of numerous, challenging efforts. It is cheerfully and proudly dedicated to the people who serve as an inspiration. Thanks to our inspiring supervisor, seniors, classmates and friends who offered assistance when there were obstacles with the project.

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List of Acronyms

FDA	United States Food and Drug Administration
AKI	Acute Kidney Injury
FAERS	Food and Drug Administration's (FDA) Adverse Event Reporting System
VAERS	Vaccine Adverse Event Reporting System
ICSRs	Individual Case Safety Reports
MedDRA	Medical Dictionary for Regulatory Activities
ICH	International Conference on Harmonization
ADRs	Adverse Drug Reactions
PTs	Preferred Terms
FPVD	French Pharmacovigilance Database
ROR	Reporting Odds Ratio
CI	Confidence Interval
PRR	Proportional Reporting Ratio
DILI	Drug-Induced Liver Injury

Chapter 1

Introduction

1.1 Onychomycosis

Recent surveys have estimated the prevalence of onychomycosis to be 10% worldwide, most likely as a result of lifestyle changes and aging (Gupta et al., 2020; Thomas et al., 2010). Onychomycosis has been reported to affect about one-third of diabetic patients (Thomas et al., 2010). Clinically, the disease is divided into five different types: candidal onychomycosis, distal and lateral subungual onychomycosis, proximal subungual onychomycosis, superficial white onychomycosis, and total dystrophic onychomycosis (Shirwaikar et al., 2008). The disease is more prevalent in toenails and is more usually observed in males (Sigurgeirsson & Baran, 2014). Dermatophytes, most often *Trichophyton rubrum* (*T. rubrum*), is discovered to be the primary causative agent of the disease. Additionally, mixed infection types and non-dermatophyte mold infections are also discovered (Gupta et al., 2020). Onychomycosis can significantly negatively impact one's quality of life, thus the condition should not be underestimated (Sigurgeirsson et al., 2002). Prior to starting treatment for onychomycosis, confirmatory tests should be carried out. It is essential to collect sufficient and adequate samples in order to identify the specific etiological fungus (Singal & Khanna, 2011). For assessment, direct microscopy, fungus culture, and histopathology can be used. Moreover, the infectious organism can be quickly identified using polymerase chain reaction (Lipner & Scher, 2019a).

1.2 Current Treatment Strategies for the Management of Onychomycosis

Eradication of the organism demonstrated in the diagnostic tests is the primary aim of treatment. The success of systemic therapy is usually always greater than that of topical therapy (Roberts et al., 2003). Topical therapy includes ciclopirox olamine, efinaconazole, and the nonprescription topical solution containing propylene glycol-urea-lactic acid. On the other hand, terbinafine, fluconazole, and itraconazole are administered systemically (Rosen & Stein Gold, 2016). When compared to intermittent itraconazole, continuous terbinafine offered better long-term mycological and clinical efficacy as well as lower rates of mycological and clinical relapse (Sigurgeirsson et al., 2002).

1.3 Safety and Efficacy of Oral Terbinafine, Fluconazole, Ravuconazole, and Oteseconazole in the Treatment of Onychomycosis

Oral terbinafine was allowed for the treatment of onychomycosis by the United States Food and Drug Administration (FDA) in a dosage regimen of 250 mg per day for 12 weeks as it was proved more effective than azole antifungals, showing a 38% complete cure rate (Kreijkamp-Kaspers et al., 2017; Rosen & Stein Gold, 2016). The drug has fewer drug interactions, but dosage adjustments are needed for cimetidine, cyclosporin, warfarin, theophylline, and tricyclic antidepressants (Iorizzo et al., 2005). Headache, rash, and increased liver enzymes are some of its adverse effects (Shirwaikar et al., 2008). Terbinafine requires monitoring of liver function in case of long-term therapy due to its tendency to cause idiosyncratic liver and skin reactions (Roberts et al., 2003).

Fluconazole is less effective compared to terbinafine and itraconazole in the treatment of onychomycosis, and thus the drug is prescribed for the patients who are intolerant to the other agents (Brown, 2009). For the treatment of onychomycosis, oral fluconazole at a dose of 50 mg per day, or 300 mg per week is advised. For fingernails and toenails, the course of treatment

lasts for ≥ 6-12 months, respectively (Iorizzo et al., 2005). The FDA has not approved fluconazole for the treatment of onychomycosis because it has a greater relapse rate than terbinafine and itraconazole (Rosen & Stein Gold, 2016; Vora et al., 2014). In onychomycosis treatment efficacy rates of 37% with 150 mg per week, 46% with 300 mg per week, and 48% with 450 mg per week are reported (Scher et al., 1998). As side effects, it disrupts the gastrointestinal system and inhibits cytochrome P450 (CYP 3A4 and 2C9). Terfenadine and astemizole is contraindicated with fluconazole. Tricyclic antidepressants, cisapride, hydrochlorothiazide, rifampicin, tolbutamide, zidovudine, and warfarin need their dosages adjusted (Iorizzo et al., 2005).

Oral ravuconazole is reported to be more effective against *Rhizopus* species than voriconazole in a study on clinical isolates of filamentous fungus. It is extremely potent against various *Aspergillus* species (91 to 94%) (Pfaller et al., 2002). The drug has encouraging outcomes in the treatment of onychomycosis. Ravuconazole prodrug BFE1224 exhibits efficacy at 200 mg per day for 12 weeks (Yamaguchi, 2016). However, 73% of patients in a phase II trial using ravuconazole to treat onychomycosis experienced adverse effects from the drug, which included dizziness, anemia, diarrhea, and urinary incontinence (Yan et al., 2006).

In a 60-week, randomized, double-blind, placebo-controlled, multicenter, phase II trial, 259 adults with moderate-to-severe distal and lateral subungual onychomycosis of the toenail received oral oteseconazole (300 mg for 12 weeks or 600 mg for 24 weeks) and experienced high nail clearance rates. Ingrown toenails, dermatitis, and headache were the most commonly mentioned treatment-emergent adverse events (Hoy, 2022).

1.4 Relation to Oral Terbinafine, Fluconazole, Ravuconazole, and Oteseconazole with Hepatotoxicity and Acute Kidney Injury (AKI)

According to several reports, terbinafine can result in cholestasis, acute hepatitis, acute liver failure, vanishing bile duct syndrome, and severe jaundice, among other types of hepatotoxicity (Choudhary et al., 2014; Fernandes et al., 1998). Between 1:45,000 and 1:54,000 cases experience the onset of such conditions (Ajit et al., 2003). Jaundice often appears 2–6 weeks following drug administration, and discontinuing terbinafine causes the disease to return to normal in 2–12 months (Choudhary et al., 2014). However, in one incident, the patient required an orthotropic liver transplant after experiencing fulminant hepatic failure 4 weeks after the treatment (Ajit et al., 2003).

Fluconazole has the propensity to cause hepatotoxicity, as demonstrated by histopathologic alterations and case reports. Patients with kidney impairment who are severely ill are particularly vulnerable to it (Gadour & Kotb, 2021; Khoza et al., 2017). According to reports, the condition affects 1.9% of the patients using the medication (Girois et al., 2005). Furthermore, fluconazole-induced liver injury has been observed to occur in 316 out of 100,000 individuals in Taiwan (Manning et al., 1980). It is discovered to be non-dose dependent and caused by an idiosyncratic reaction, despite numerous hypotheses on fluconazole's toxic metabolites and its potential to cause hepatocyte mitochondrial disease (Chana et al., 2014).

By far, there has not been any evidence of ravuconazole-induced hepatotoxicity in non-clinical trials among animals (Petraitiene et al., 2004) and otesaconazole affecting liver function (Hoy, 2022).

A case of a 22-year-old-male taking terbinafine for tinea was found to develop rhabdomyolysis and acute kidney injury (AKI) within 9 days of the treatment. Upon immediate discontinuation

of terbinafine and proper treatment of the condition by hemodialysis, the kidney function turned back to normal in a month (Zhou & Bagga, 2020).

Fluconazole can cause AKI in critically ill patients (Patel et al., 2011) although a replacement of amphotericin B liposomal with 800 mg oral fluconazole in a 42-year-old male suffering from *Coccidioides posadasii* meningoencephalitis has been shown to improve the patient's condition who developed amphotericin B liposomal induced AKI. However, this high dose of fluconazole was further found to be associated with fluconazole-related limb and trunk alopecia (Lang et al., 2019).

Moreover, severely ill patients are more prone to develop voriconazole-induced AKI. But such cases are not found in terms of ravuconazole and in oteseconazole (Iorizzo et al., 2010).

1.5 Oral Terbinafine

Terbinafine, an allylamine-group antifungal drug, was initially approved for the treatment of onychomycosis in the UK and the USA in the 1990s (Krishnan-Natesan, 2009). It has been shown to be more effective and safe than griseofulvin, itraconazole, and fluconazole in treating dermatophytoses and toenail onychomycosis in several randomized, controlled trials (Elewski & Hay, 1996). Terbinafine has a primary fungicidal effect on S. schenckii, dermatophytes, and other filamentous fungi (Petranyi et al., 1987).

1.5.1 Pharmacokinetics

1.5.1.1 Absorption

Terbinafine is well absorbed from the gastrointestinal tract in more than 70% of doses taken orally. Food does not substantially impact its bioavailability (Gupta & Shear, 1997). Healthy participants experienced maximal plasma concentrations of about 0.9 mg/L after a single dose

of 250 mg of terbinafine within 2 hours. Following a single dose of 250 mg, mean AUC values of 3.1 to 3.6 mg*h/L were observed (Balfour & Faulds, 1992).

1.5.1.2 Distribution

Following a 250 mg oral terbinafine dose in healthy volunteers, the mean volume of distribution in a 2-compartment model was calculated to be 220.6 L for the central compartment and 726.9 L for the peripheral compartment (Balfour & Faulds, 1992). The drug shows high keratinophilic and lipophilic activity (Gupta & Shear, 1997) with strong and nonspecific binding affinity to plasma proteins (Jensen, 1989). It crosses the blood-brain barrier at levels higher than expected from the free fraction available (Machard et al., 1989). It is widely distributed throughout the stratum corneum, sebum, hair, dermis, epidermis, and nails in addition to adipose tissue (Balfour & Faulds, 1992; Gupta & Shear, 1997). Terbinafine rapidly accumulates in sebum (45.1 mg/kg), the stratum corneum (9.1 mg/kg), and hair (2.6 mg/kg) (Balfour & Faulds, 1992).

A 250mg/day dose of the drug is observed to be available in distal clippings of diseased toenails or fingernails within 3 to 18 weeks of beginning the therapy, based on a nail matrix kinetics research. The mean concentration of terbinafine in the target nails stayed between 0.25 and 0.55 ng/mg. This shows that terbinafine may significantly shorten the typical treatment duration for onychomycosis (6 months for fingernails and 12 months for toenails) (Finlay et al., 1990).

1.5.1.3 Metabolism

Terbinafine is rapidly broken down by cytochrome P-450, which uses it as a substrate (Gupta & Shear, 1997). The most significant enzymes for overall metabolism are CYP2C9, CYP1A2, and CYP3A4 (Vickers et al., 1999). All the metabolites have been shown to be inactive (Gupta & Shear, 1997).

1.5.1.4 Elimination

With a clearance rate of 76 L/h in healthy volunteers (Darkes et al., 2003), terbinafine has an elimination half-life of around 16 hours and a terminal half-life of roughly 80 to 100 hours (Leyden, 1998). Terbinafine is eliminated in the urine at 80% and the remainder through feces (Darkes et al., 2003).

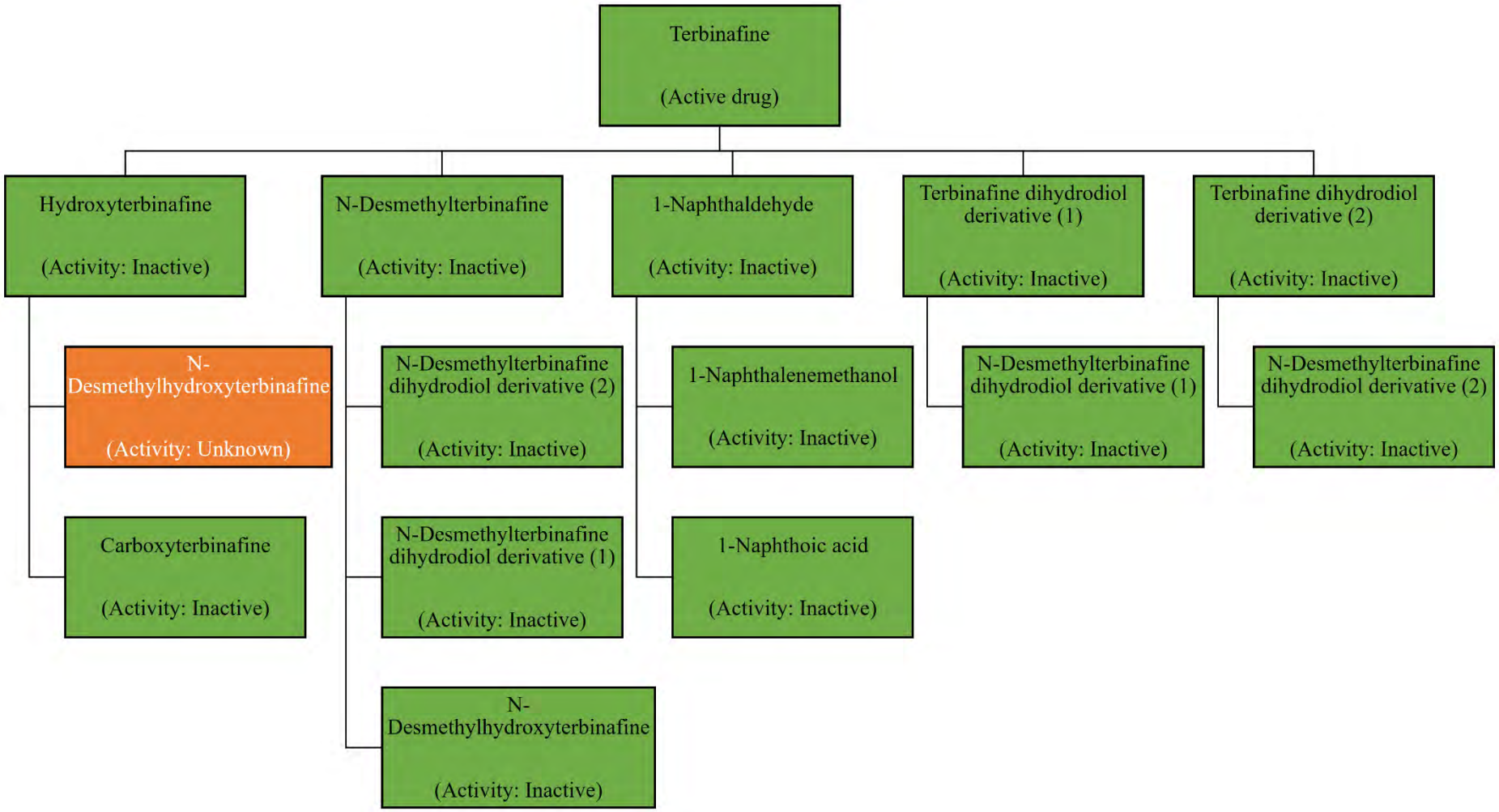

Figure 1: Metabolism of oral terbinafine (Vickers et al., 1999; Zhou et al., 2009).

1.5.2 Mechanism of Action

Terbinafine shows broad-spectrum activity against dermatophytes, and against NDMs, and Candida species by inhibiting squalene epoxidase (Lipner & Scher, 2019b). All steroids have squalene as their precursor, a consecutive conversion of which leads to the formation of ergosterol. Ergosterol is the primary fungal sterol that promotes growth and proliferation (Jorda & Puig, 2020). Hence, the administration of terbinafine causes a toxic buildup of squalene and a reduction in ergosterol synthesis in vitro. Terbinafine's minimal inhibitory concentrations for dermatophytes are almost equal to its minimal fungicidal concentrations (Leyden, 1998).

1.6 Oral Fluconazole

Fluconazole is a first-generation triazole which contrary to prior azole antifungals containing imidazole ring, comprises a triazole ring. These modifications improve the drug's selectivity, metabolic stability, and water solubility (Hollier & Cox, 1995). The medication has been proven to be effective in treating onychomycosis in vitro, as well as aspergillosis, coccidioidomycosis, histoplasmosis, cryptococcosis, blastomycosis, systemic phaeohyphomycosis, and candidiasis (Hollier & Cox, 1995; Scher et al., 1998). In 1988, the drug first was first made available for commercial use (Fischer & Ganellin, 2006).

1.6.1 Pharmacokinetics

1.6.1.1 Absorption

Fluconazole is water-soluble and rapidly absorbed from the digestive tract in 80–90% of the dose in a linearly proportionate manner to the dose. A 150-mg dose of the drug reaches its peak plasma concentration of 2.44-3.58 g/ml within 2 hours. The time it takes to reach the maximum serum concentration is prolonged by the presence of food until 4 hours after the dose (Hollier

& Cox, 1995). The mean AUC of fluconazole in healthy volunteers receiving 25 mg of the drug was 20.3 mg*h/L (Debruyne & Ryckelynck, 1993).

1.6.1.2 Distribution

Fluconazole has a broad range of distribution and is present in cerebrospinal fluid, dialysis fluid, and other fluids. This enables it to treat a number of systemic fungal diseases, including coccidioidal meningitis and fungal peritonitis (Debruyne & Ryckelynck, 1993). Drug penetrations into the skin and nails have also been seen (Hollier & Cox, 1995). Fluconazole's volume of distribution is highest during the neonatal period (1.18 to 2.25 L/kg) and declines by young adulthood to a value that is comparable to that observed for adults (0.7 L/kg) (Brammer & Coates, 1994). Its plasma protein binding is 12%, and the apparent volume of distribution is 0.7 L/kg (Brammer et al., 1990).

1.6.1.3 Metabolism

Fluconazole undergoes around only 10% metabolism (Bruggemann et al., 2009). In one study, only three of the drug's metabolites (4% of the total drug administered) were identified in dogs and mice (Humphrey et al., 1985). In a different experiment, two metabolites were identified in healthy volunteers: a fluconazole N-oxide metabolite (2%), and a glucuronidated metabolite on the hydroxyl moiety (6.5%) (Brammer et al., 1991). Fluconazole is a strong inhibitor of CYP2C19 and a moderate inhibitor of CYP3A4 (Desai, 2016).

1.6.1.4 Elimination

The primary route of elimination of fluconazole is the kidney since 80% of the administered drug is detected in urine as an unchanged form (Brammer et al., 1991). The half-life in patients with normal renal function is observed to be 31 hours and the mean plasma clearance is 0.23 ml/min/kg (Brammer et al., 1991; Hollier & Cox, 1995).

1.6.2 Mechanism of Action

Fluconazole selectively inhibits the cytochrome P450-dependent enzyme lanosterol 14-demethylase found in fungi (Hollier & Cox, 1995). An iron atom in the heme group of the enzyme lanosterol 14-demethylase forms a bond with the free nitrogen atom on the azole ring of fluconazole (Joseph-Horne & Hollomon, 1997). Lanosterol 14-demethylase is required for the conversion of lanosterol to ergosterol, a major component of the fungal cell membrane. Ergosterol synthesis is disrupted, and as a result, the membrane undergoes structural and functional alterations that make the fungus more vulnerable to osmotic and immune-mediated damage and hinder cell adhesion (Hollier & Cox, 1995).

1.7 Oral Ravuconazole

Ravuconazole, an isomer of isavuconazole, is a triazole antifungal that is at present undergoing clinical trials (Petraitiene et al., 2004). For the oral treatment of onychomycosis, ravuconazole and its prodrugs (especially BFE1224) are potential novel therapeutic candidates, showing effectiveness at a dose of 200 mg/day for 12 weeks (Yamaguchi, 2016). A wide range of antifungal action is demonstrated by the drug. In vitro tests suggest that it has strong antifungal activity against multiple *Candida* spp., *Aspergillus* spp., and *Cryptococcus* neoformans (Petraitiene et al., 2004). However, it shows limited activity against *Zygomycetes* spp., *Scedosporium* spp., and *Fusarium* spp. (Chackalamannil et al., 2017).

1.7.1 Pharmacokinetics

1.7.1.1 Absorption

The oral intake of ravuconazole results in rapid absorption (Yamaguchi, 2016). In a non-clinical experiment, doses of 2.5, 5.0, and 10 mg/kg/day were administered to rabbits experiencing invasive pulmonary aspergillosis. The mean C_{max} was found to be 2.7, 7.96, and

13.88 µg/ml, respectively. Furthermore, the AUC_{0-24} was determined to be 20, 28, and 68.66 µg*h/ml, respectively (Petraitiene et al., 2004). The t_{max} in disease-free rats receiving oral ravuconazole 10 mg/kg is discovered to be 8 hours, where the C_{max} was 1.68 µg/ml (Mikamo et al., 2002). When ravuconazole was taken along with a high-fat meal, a 2- to 4-fold rise in systemic bioavailability was seen (Yamaguchi, 2016).

1.7.1.2 Distribution

Although poorly soluble in water (0.6 μgmL^{-1}) (Triggle & Taylor, 2006), ravuconazole exhibits significant protein binding (98%) (Yamaguchi, 2016). In comparison to similar blood levels, ravuconazole concentrations in rat lung and uterus tissues were found 2–6 times greater (Mikamo et al., 2002).

1.7.1.3 Metabolism

Cytochrome P450 enzymes are thought to play a role in the metabolism of ravuconazole (Yamaguchi, 2016). Unlike other azoles, the drug does not significantly inhibit the CYP 3A4 metabolic pathway (Baran et al., 2005).

1.7.1.4 Elimination

Ravuconazole has a relatively longer terminal half-life (4–8 days) throughout clinical trials, and it is predominantly eliminated in feces (Yamaguchi, 2016).

1.7.2 Mechanism of Action

Ravuconazole also inhibits cytochrome P450 14a-demethylase, an enzyme necessary for the formation of ergosterol, like other azole antifungals (Shin et al., 2000).

1.8 Oral Otesaconazole

Otesaconazole, also known as VT-1161, is a novel, selective inhibitor of the fungal enzyme CYP51 and exhibits antifungal action against *Candida albicans*, which is sensitive to fluconazole (Garvey et al., 2015). In April 2022, the US Food and Drug Administration (FDA) approved the drug for the management of recurrent vulvovaginal candidiasis (Hoy, 2022). In the treatment of onychomycosis, otesaconazole had a promising clinical outcome and an acceptable adverse event profile (Elewski et al., 2021).

1.8.1 Pharmacokinetics

1.8.1.1 Absorption

Otesaconazole has a high oral absorption rate, which is confirmed by non-clinical study results showing a high bioavailability (Sobel & Nyirjesy, 2021). However, high-calorie and high-fat diets have an impact on bioavailability. In the treatment of vulvovaginal candidiasis, otesaconazole's mean C_{max} was found to be 2.8 g/mL within 5 to 10 hours of dosing. In that case, the AUC was 64.2 g*h/mL (Mycovia Pharmaceuticals, 2022).

1.8.1.2 Distribution

Oteseconazole generally has a 423 L volume of distribution and a strong protein binding of between 99.5 and 99.7% (Mycovia Pharmaceuticals, 2022).

1.8.1.3 Metabolism

No major metabolism is involved with oteseconazole (Mycovia Pharmaceuticals, 2022).

1.8.1.4 Elimination

Oteseconazole has a median terminal half-life of around 138 days, which is longer than most other drugs (Mycovia Pharmaceuticals, 2022). The excreted medication is primarily found in bile and feces, with trace amounts being present in urine (Sobel & Nyirjesy, 2021).

1.8.2 Mechanism of Action

Otesaconazole prevents the production of ergosterol by selectively inhibiting the fungal CYP51 (also known as 14-demethylase) (Garvey et al., 2015). Furthermore, it causes fungal cell death by increasing the buildup of 14-methylated sterols (Mycovia Pharmaceuticals, 2022).

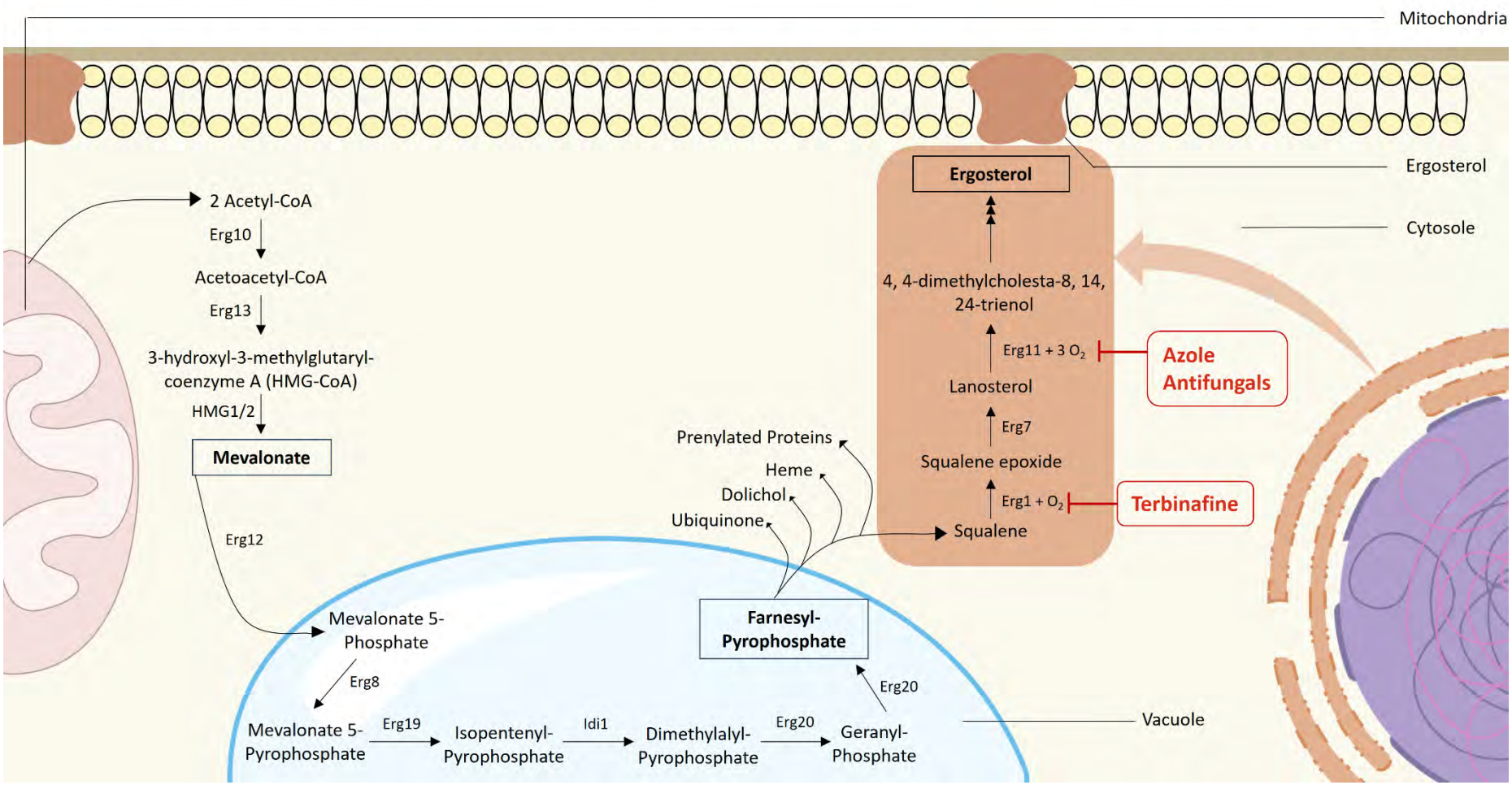

Figure 2: Biosynthesis of ergosterol and terbinafine and azole antifungals' mechanism of action (Jorda & Puig, 2020)

Table 1: Pharmacokinetics of oral terbinafine, fluconazole, ravuconazole and oteseconazole (Balfour & Faulds, 1992; Brammer et al., 1991; Brammer et al., 1990; Bruggemann et al., 2009; Darkes et al., 2003; Debruyne & Ryckelynck, 1993; Desai, 2016; Gupta & Shear, 1997; Hollier & Cox, 1995; Hosseini-Yeganeh & McLachlan, 2002; Jensen, 1989; Leyden, 1998; Machard et al., 1989; Mikamo et al., 2002; Mycovia Pharmaceuticals, 2022; Petraitiene et al., 2004; Sobel & Nyirjesy, 2021; Vickers et al., 1999; Yamaguchi, 2016)

Pharmacokinetic Parameters		**Terbinafine**	**Fluconazole**	**Ravuconazole**	**Oteseconazole**
Absorption	Bioavailability	70% absorbed in the GIT.	80% - 90% absorbed in the GIT.	High bioavailability.	High bioavailability.
	C_{max}	0.9 mg/L.	2.44-3.58 g/ml.	1.68 µg/ml.	2.8 g/mL.
	T_{max}	2 hours.	2 hours.	8 hours.	5-10 hours.
	AUC	3.1 to 3.6 mg*h/L.	20.3 mg*h/L.	68.66 µg*h/ml.	64.2 g*h/mL.
	Effect of food on bioavailability	Not affected.	Gets prolonged until 4 hours after the dose.	2- to 4-fold rise in systemic bioavailability is achieved with a high-fat meal.	C_{max} and $AUC_{0\text{-}72h}$ get 45% and 36% higher, respectively with a high-calorie and high-fat diet.

Distribution	V_D	780 - 2000 L.	0.7 L/kg in adults.	Unknown.	423 L.
	Plasma protein binding	Binds non-specifically.	12%.	98%.	99.5-99.7%.
	Blood-brain barrier crossing	Yes.	Yes.	Unknown.	Unknown.
Metabolism		Metabolized primarily in the liver by CYP2C9, CYP1A2, and CYP3A4.	Undergoes around only 10% metabolism. It's a strong inhibitor of CYP2C19 and a moderate inhibitor of CYP3A4.	Cytochrome P450 enzymes are thought to play a role in the metabolism of ravuconazole.	No major metabolism is involved with oteseconazole.
Elimination	Clearance	76 L/hour.	0.23 ml/min/kg.	Unknown.	Clearance was 48% higher in non-white people than it was in white participants.
	Half-life	16 hours.	31 hours.	4–8 days.	Around 138 days.

	Route of elimination	Eliminated in the urine at 80% and the remainder through feces.	The primary route of elimination is the kidney since 80% of the drug gets eliminated through urine.	Predominantly eliminated in feces.	Primarily excreted through bile and feces, and a trace amounts is found in urine.

$AUC_{(0–24\ hour)}$: area under the curve from time 0–24 hour; C_{max}: maximum plasma concentration; T_{max}: time to reach C_{max}; V_D: volume of distribution.

Chapter 2

Methodology

2.1 Data Source

In phase IV clinical trial of a drug, the true safety and efficacy of a drug is assessed through ongoing safety monitoring via a system for tracking spontaneous adverse events or via post-marketing surveillance, making it a crucial stage of the drug development process. Frequently occurring practice patterns can produce leads that can give rise to a further review of a potential indication or a signal that can call for regulatory action (Suvarna, 2010). Thus, regulatory bodies have developed systems and databases for monitoring drugs' adverse events. For instance, the FDA Adverse Event Reporting System (FAERS) and the Vaccine Adverse Event Reporting System (VAERS), Vigibase, the WHO's global database of individual case safety reports (ICSRs), EudraVigilance, which was formed in partnership with the European Union Member States, etc. (Bihan et al., 2020).

In our case, the information used to identify the signal was gathered from the FAERS database, a public repository for reports of adverse events, prescription errors, and product quality issues that led to adverse events that were sent to the FDA. According to medication information, patient demographics and administrative data, adverse effects, sources of reports, the beginning and end of therapy, indication, and patient outcome, the FAERS database is set up. The Medical Dictionary for Regulatory Activities (MedDRA) informatic framework is used to code the adverse event information in FAERS. Additionally, its information structure follows the International Conference on Harmonization's guidelines (ICH). Moreover, this system provides user-friendly statistics and visualizations and makes it easier to query the data (Center for Drug Evaluation and Research, 2021).

2.2 Inclusion and Exclusion Criteria

In the investigation, FAERS data from January 2016 to September 2022 were included and the following generic names were used: terbinafine, fluconazole, ravuconazole, and otesaconazole. FAERS defines adverse drug reactions (ADRs) using Preferred Terms (PTs) from the MedDRA (MedDRA, n.d.). 'Hepatotoxicity' and 'acute kidney injury' were two PTs used in our study to assess antifungal-induced liver and kidney injury respectively. We excluded all the data where a number of other suspected drugs are present. The possible duplication of data was cautiously excluded by using the case number. The age, sex, and event date were matched as another method of removing duplicate reports. Primarily, onychomycosis was focused as the indication of oral terbinafine, fluconazole, revuconazole, and otesaconazole. Isoniazid and gentamicin were chosen as known hepatotoxicity and AKI-causing agents as ADRs respectively.

Isoniazid is globally known as a drug, causing hepatotoxicity as an adverse effect. It also causes acute liver injury with jaundice, which is also found to be fatal. Even if the adverse effect is self-limited, certain cases of jaundice required an emergent liver transplant (National Institute of Diabetes and Digestive and Kidney Diseases (U.S.) & National Institute of Diabetes and Digestive and Kidney Diseases (U.S.), 2012). Moreover, this is reported as the most common agent (14 times more than other drugs) causing hepatotoxicity in Uganda (Nanyonga et al., 2022; Russom et al., 2018). Its reason for developing hepatotoxicity is related to the drug's plasma concentration level, and the correlation has been established (Jeong et al., 2015).

On the other hand, a study based on the French national pharmacovigilance database (FPVD) compared drug-induced AKI among diuretics, anti-inflammatory agents, antineoplastic drugs, drugs affecting the renin-angiotensin system, as well as antibacterial drugs and found gentamicin having one of the highest reporting odds ratio (ROR) (Pierson-Marchandise et al., 2017). By preventing protein synthesis in renal cells, gentamicin causes AKI. This leads them

to necrosis, which preferentially affects cells in the proximal renal tubule and leads to acute tubular necrosis. This is further followed by acute renal failure (Balakumar et al., 2010).

Based on these cases and evidence, isoniazid and gentamicin were selected as known AKI and hepatotoxicity-causing agents as ADRs, respectively.

2.3 Endpoints

The end points for this project are hepatotoxicity and AKI. The endpoints are specified using PTs of MedDRA.

2.4 Statistical Analysis

For signal detection, disproportionality analysis was done by computing ROR in R software (version 4.2.1) and corresponding 95% confidence interval (CI) for the reporting association between adverse effects (hepatotoxicity and AKI) and each of the drugs which included terbinafine, fluconazole, ravuconazole, oteseconazole. ROR was chosen due to its advantageousness over the proportional reporting ratio (PRR) in terms of estimating relative risk and eliminating biases (Rothman et al., 2004). The ROR was determined by using a 2×2 contingency table, where reports were classified based on the presence or absence of oral terbinafine, fluconazole, ravuconazole and otesaconazole, and the adverse effects (hepatotoxicity and AKI). Using the formula of $\frac{A.D}{B.C}$, the ROR was calculated. When the lower limit of the 95% confidence interval for the adjusted ROR was greater than 1, it was determined that the adverse effects were significantly more frequently reported than they were after using the other medicines, which is also referred to as a signal in pharmacovigilance study (Hauben & Aronson, 2009). Moreover, ROR for isoniazid and gentamicin was also calculated as a control apart from oral terbinafine, fluconazole, ravuconazole, and otesaconazole to compare the significance of the signals produced by them.

Chapter 3

Results

3.1 Signal Detection

3.1.1 Hepatotoxicity

Regarding causing hepatotoxicity, terbinafine showed the highest ROR (95% CI) of 5.20 (2.70, 10.01) among the drugs. Following that, fluconazole showed a ROR (95% CI) of 1.15 (0.58, 2.31). There were no cases found for ravuconazole and otesaconazole-induced hepatotoxicity in the FAERS database.

We used the whole database as a comparator where reports from January 2016 to September 2022 were collected. In terms of terbinafine, 9 reports were found causing hepatotoxicity and 2392 other cases were found of it causing other adverse effects. The ROR (95% CI) of terbinafine was then determined to be 5.20 (2.70, 10.01). That means, according to the condition, terbinafine is showing a signal.

In the calculation of ROR (95% CI) of fluconazole causing hepatotoxicity, the entire database used as a comparator, containing reports from January 2016 to September 2022, was collected as a comparator, as we followed previously. Fluconazole was linked to 8 cases of hepatotoxicity, and 9587 reports of other side effects. Through the calculation, it was determined that fluconazole's ROR (95% CI) was 1.15. (0.58, 2.31). This indicates that fluconazole is not producing a signal for the adverse effect.

Finally, the ROR of isoniazid causing hepatotoxicity was determined as a control to compare the ROR of the drugs using reports from January 2016 to September 2022 in the whole database. There were 62 cases of the adverse effect and 4991 cases of other adverse events caused by isoniazid reported. The ROR (95% CI) of isoniazid is calculated to be 17.26 (13.43,

22.19). This clearly shows a signal and it is determined to be 3.32 times more hepatotoxic compared to terbinafine, and 15.01 times more than fluconazole.

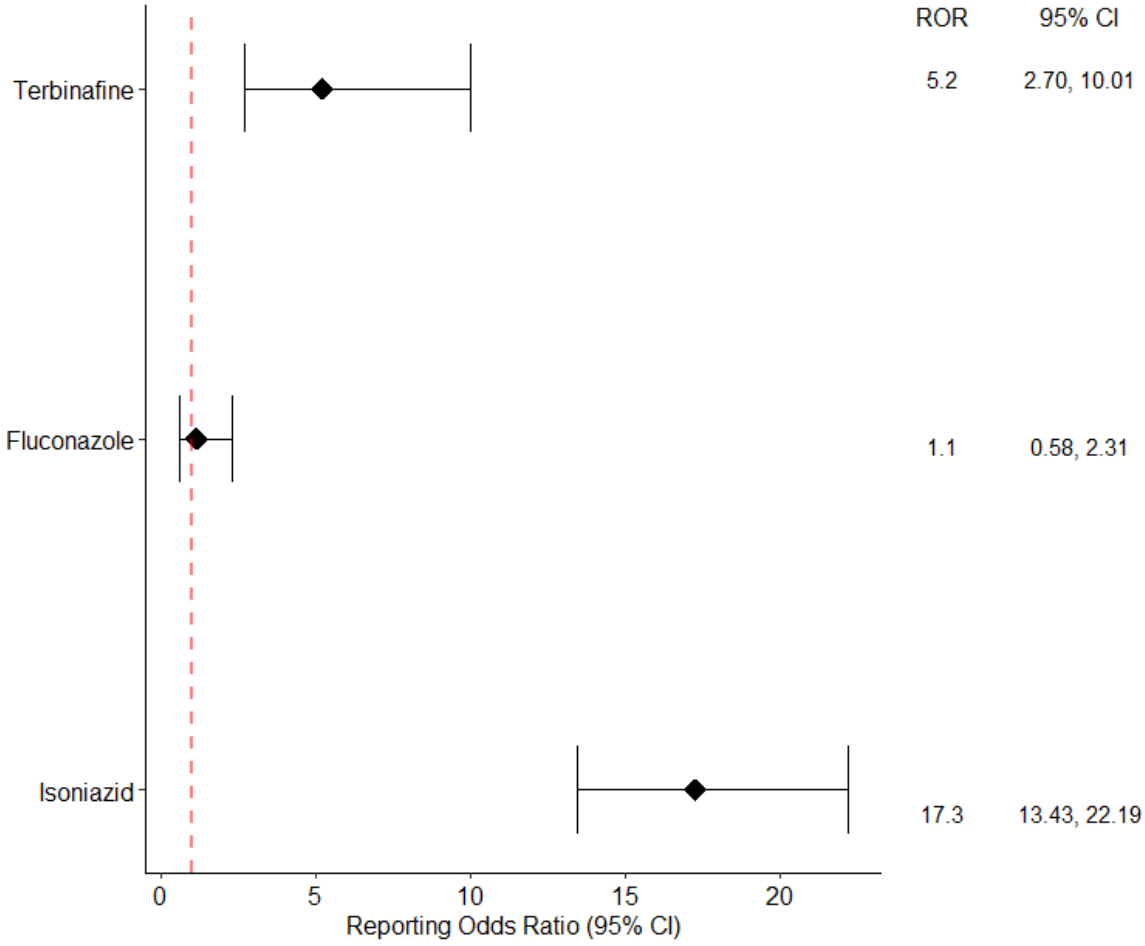

Figure 3: Forest Plot for hepatotoxicity of oral terbinafine and fluconazole against the whole database where isoniazid is used as a control

3. 1. 2 Acute Kidney Injury (AKI)

None of the antifungals displayed any signal that they could cause AKI. There were 9 reports of AKI caused by terbinafine, and 28 cases of the same adverse effect were reported for fluconazole. And the drugs were identified to have ROR (95% CI) values of 0.53 (0.27, 1.02) and 0.41 (0.28, 0.60), respectively for terbinafine and fluconazole. Like hepatotoxicity, no cases were found for ravuconazole and oteseconazole induced AKI in the FAERS database.

As a final step, the ROR of gentamicin resulting in AKI was established as a control. 50 cases of the adverse effect and 3264 cases of other adverse events brought on by gentamicin were recorded in the entire database from January 2016 to September 2022. Gentamicin's ROR (95% CI) is calculated to be 2.15 (1.63, 2.84). The calculation displays a signal for gentamicin causing AKI and the drug is found to be 4.06 times more AKI causing agent than terbinafine and 5.24 times more than fluconazole.

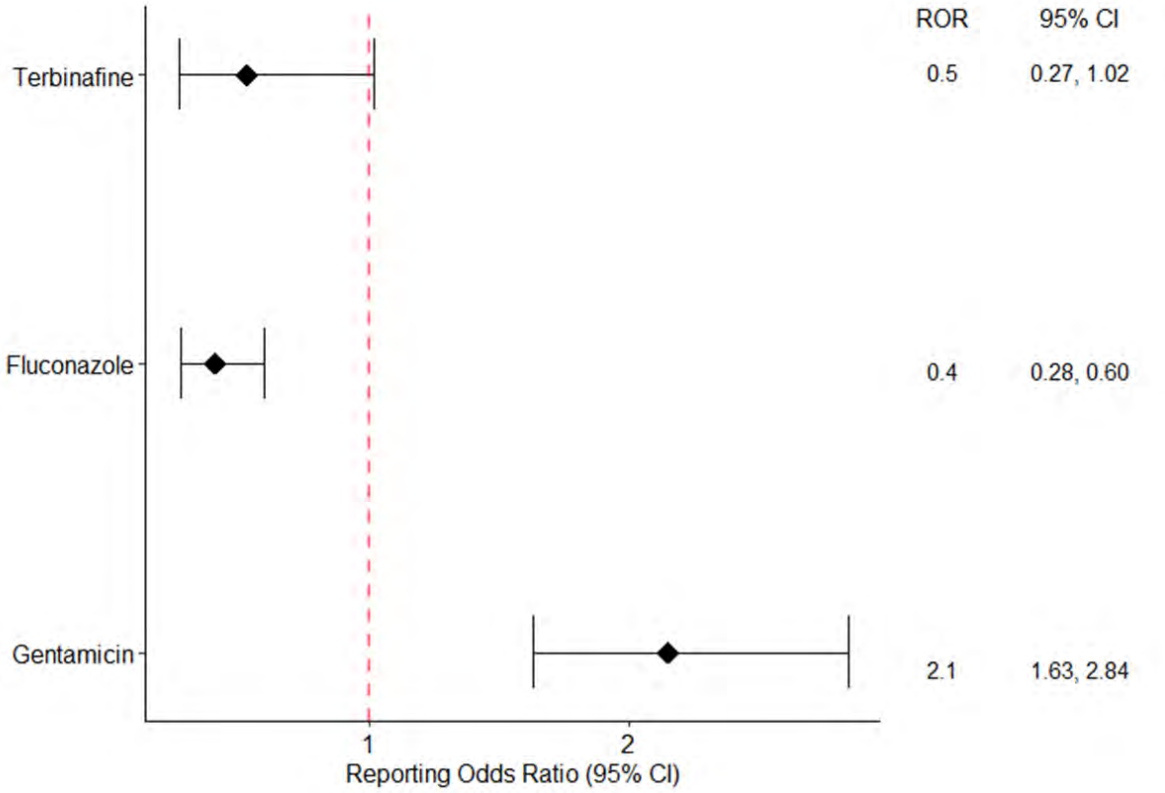

Figure 4: Forest Plot for AKI of oral terbinafine and fluconazole against the whole database where gentamicin is used as a control

Table 2: ROR of oral terbinafine, fluconazole, and control drugs (isoniazid, gentamicin) in causing hepatotoxicity and AKI

Drugs	**Cases (hepatotoxicity)**	**Cases (AKI)**	**ROR (95% CI) (hepatotoxicity)**	**ROR (95% CI) (AKI)**
Oral Terbinafine	9	9	5.20 (2.70, 10.01)	0.53 (0.27, 1.02)
Oral Fluconazole	8	28	1.15 (0.58, 2.31)	0.41 (0.28, 0.60)
Isoniazid	62	N/A	17.26 (13.43, 22.19)	N/A
Gentamicin	N/A	50	N/A	2.15 (1.63, 2.84)

Chapter 4

Discussion

The results of our experiment suggest a significant association with hepatotoxicity by terbinafine. There were 9 cases among 2392 adverse events of terbinafine causing hepatotoxicity and 8 among 9587 cases were found for fluconazole in the FAERS database. Furthermore, the drugs' tendency to cause hepatotoxicity was compared with isoniazid, and it is found to be 3.32 times more hepatotoxic compared to terbinafine, and 15.01 times more than fluconazole. Considering that only 1:45,000 to 1:54,000 cases of hepatic dysfunction were recorded, terbinafine-induced hepatotoxicity was not thought to be clinically important (Ajit et al., 2003; Fernandes et al., 1998). Even though it is a less common side effect with a frequency of 2.5 occurrences per 100,000, terbinafine can induce acute or sub-acute liver failure necessitating a liver transplant (Choudhary et al., 2014; Ly et al., 2019). Our investigation suggests a strong association of terbinafine and hepatotoxicity. Hence its long-term usage should be carefully monitored.

The time between terbinafine exposure and the beginning of jaundice is typically 2–6 weeks. It may take up to three weeks for serum bilirubin levels to peak after discontinuing terbinafine, and it can take two to twelve months for liver function tests to return to normal (Choudhary et al., 2014). The drug's mechanism of causing hepatotoxicity is not established yet but cholestasis and a significant increase in liver enzymes are found. Thus, it is advised to check the liver function before starting treatment and to continue regular monitoring for 4-6 weeks after starting treatment (Yan et al., 2014).

Fluconazole has also been found to be linked to hepatic or cholestatic liver damage (Chana et al., 2014). However, our investigation found no correlation of fluconazole-induced hepatotoxicity. Hepatocyte mitochondrial disease may result from fluconazole, which can be

brought on by the suppression of cytochrome P450 enzymes in the smooth endoplasmic reticulum and inner mitochondrial membrane or by an unknown toxic drug metabolite of the drug (Guillaume et al., 1996; Somchit et al., 2002). Fluconazole-induced hepatotoxicity was previously found to start between days 6 and 25 of treatment. However, the majority of patients indicated a delayed onset at least a week following the start of fluconazole treatment (Chana et al., 2014).

Our investigation also found no relation between terbinafine-, and fluconazole-induced AKI. So far, only a few cases of terbinafine and fluconazole induced AKI has been reported (Lang et al., 2019; Zhou & Bagga, 2020). But cases of ravuconazole and otesaconazole induced hepatotoxicity are not found in terms of ravuconazole and in oteseconazole (Hoy, 2022; Iorizzo et al., 2010; Petraitiene et al., 2004).

4.1 Limitation

FAERS database, however, has some limitations of its own. For instance, it's not certain that the incident that was reported was brought on by the product. The database cannot prove a connection between a drug's effects and an adverse effect. Additional limitations include inadequate reports, or reports without clear causal relationships (Center for Drug Evaluation and Research, 2021).

Chapter 5

Conclusion

The study confirms the relationship between hepatotoxicity and terbinafine through detecting a signal of the drugs' causing the adverse effect. The severity of the adverse effect by the drugs were determined by comparing them with isoniazid, the most hepatotoxicity-causing agent based on the available evidence. Furthermore, this study confirms terbinafine, fluconazole, ravuconazole, and oteseconazole to be safe in terms of causing AKI. Terbinafine and fluconazole were found to cause AKI way less likely than gentamicin. The requirement of regular monitoring of the liver in case of treatment by the drugs is warranted.

References

Ajit, C., Suvannasankha, A., Zaeri, N., & Munoz, S. J. (2003). Terbinafine-associated hepatotoxicity. *Am J Med Sci*, *325*(5), 292-295. https://doi.org/10.1097/00000441-200305000-00008.

Balakumar, P., Rohilla, A., & Thangathirupathi, A. (2010). Gentamicin-induced nephrotoxicity: Do we have a promising therapeutic approach to blunt it? *Pharmacol Res*, *62*(3), 179-186. https://doi.org/10.1016/j.phrs.2010.04.004.

Balfour, J. A., & Faulds, D. (1992). Terbinafine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in superficial mycoses. *Drugs*, *43*(2), 259-284. https://doi.org/10.2165/00003495-199243020-00010.

Baran, R., Gupta, A. K., & Pierard, G. E. (2005). Pharmacotherapy of onychomycosis. *Expert Opin Pharmacother*, *6*(4), 609-624. https://doi.org/10.1517/14656566.6.4.609.

Bihan, K., Lebrun-Vignes, B., Funck-Brentano, C., & Salem, J. E. (2020). Uses of pharmacovigilance databases: An overview. *Therapie*, *75*(6), 591-598. https://doi.org/10.1016/j.therap.2020.02.022.

Brammer, K. W., Coakley, A. J., Jezequel, S. G., & Tarbit, M. H. (1991). The disposition and metabolism of [14C]fluconazole in humans. *Drug Metab Dispos*, *19*(4), 764-767. https://www.ncbi.nlm.nih.gov/pubmed/1680653.

Brammer, K. W., & Coates, P. E. (1994). Pharmacokinetics of fluconazole in pediatric patients. *Eur J Clin Microbiol Infect Dis*, *13*(4), 325-329. https://doi.org/10.1007/BF01974613.

Brammer, K. W., Farrow, P. R., & Faulkner, J. K. (1990). Pharmacokinetics and tissue penetration of fluconazole in humans. *Rev Infect Dis*, *12 Suppl 3*, S318-326. https://doi.org/10.1093/clinids/12.supplement_3.s318.

Brown, S. J. (2009). Efficacy of fluconazole for the treatment of onychomycosis. *Ann Pharmacother*, *43*(10), 1684-1691. https://doi.org/10.1345/aph.1M165.

Bruggemann, R. J., Alffenaar, J. W., Blijlevens, N. M., Billaud, E. M., Kosterink, J. G., Verweij, P. E., & Burger, D. M. (2009). Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. *Clin Infect Dis*, *48*(10), 1441-1458. https://doi.org/10.1086/598327.

Center for Drug Evaluation and Research. (2021, October 23). FDA Adverse Event Reporting System (FAERS) Public Dashboard. U.S. Food And Drug Administration. https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

Chackalamannil, S., Rotella, D., & Ward, S. (2017). *Comprehensive medicinal chemistry III*. Elsevier.

Chana, J. Y. M., Kiewb, C. F., & Chongc, C. P. (2014). Early onset hepatotoxicity associated with low dose fluconazole therapy in a critically ill patient: A case report. *Eastern Journal of Medicine*, *19*, 61-65.

Choudhary, N. S., Kotecha, H., Saraf, N., Gautam, D., & Saigal, S. (2014). Terbinafine induced liver injury: a case report. *J Clin Exp Hepatol*, *4*(3), 264-265. https://doi.org/10.1016/j.jceh.2014.03.040.

Darkes, M. J., Scott, L. J., & Goa, K. L. (2003). Terbinafine: a review of its use in onychomycosis in adults. *Am J Clin Dermatol*, *4*(1), 39-65. https://doi.org/10.2165/00128071-200304010-00005.

Debruyne, D., & Ryckelynck, J. P. (1993). Clinical pharmacokinetics of fluconazole. *Clin Pharmacokinet*, *24*(1), 10-27. https://doi.org/10.2165/00003088-199324010-00002.

Desai, C. (2016). Meyler's side effects of drugs: The international encyclopedia of adverse drug reactions and interactions. *Indian Journal of Pharmacology*, *48*(2), 224.

Elewski, B., Brand, S., Degenhardt, T., Curelop, S., Pollak, R., Schotzinger, R., & Tavakkol, A. (2021). A phase II, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of VT-1161 oral tablets in the treatment of patients with distal and lateral subungual onychomycosis of the toenail. *Br J Dermatol*, *184*(2), 270-280. https://doi.org/10.1111/bjd.19224.

Elewski, B. E., & Hay, R. J. (1996). Update on the management of onychomycosis: highlights of the Third Annual International Summit on Cutaneous Antifungal Therapy. *Clin Infect Dis*, *23*(2), 305-313. https://doi.org/10.1093/clinids/23.2.305.

Fernandes, N. F., Geller, S. A., & Fong, T.-L. (1998). Terbinafine hepatotoxicity: case report and review of the literature. *The American journal of gastroenterology*, *93*(3), 459-460.

Finlay, A., Lever, L., Thomas, R., & Dykes, P. (1990). Nail matrix kinetics of oral terbinafine in onychomycosis and normal nails. *Journal of Dermatological Treatment*, *1*(sup2), 51-53.

Fischer, J. n., & Ganellin, C. R. (2006). *Analogue-based drug discovery*. Wiley-VCH. Contributor biographical information http://www.loc.gov/catdir/enhancements/fy0646/2006296627-b.html.

Publisher description http://www.loc.gov/catdir/enhancements/fy0646/2006296627-d.html.

Table of contents only http://www.loc.gov/catdir/enhancements/fy0646/2006296627-t.html.

Fluconazole. (2012). In *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. https://www.ncbi.nlm.nih.gov/pubmed/31643623.

Gadour, E., & Kotb, A. (2021). Systematic Review of Antifungal-Induced Acute Liver Failure. *Cureus*, *13*(10), e18940. https://doi.org/10.7759/cureus.18940.

Garvey, E. P., Hoekstra, W. J., Schotzinger, R. J., Sobel, J. D., Lilly, E. A., & Fidel, P. L., Jr. (2015). Efficacy of the clinical agent VT-1161 against fluconazole-sensitive and -resistant Candida albicans in a murine model of vaginal candidiasis. *Antimicrob Agents Chemother*, *59*(9), 5567-5573. https://doi.org/10.1128/AAC.00185-15.

Girois, S. B., Chapuis, F., Decullier, E., & Revol, B. G. (2005). Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis. *Eur J Clin Microbiol Infect Dis*, *24*(2), 119-130. https://doi.org/10.1007/s10096-005-1281-2.

Guillaume, M. P., De Prez, C., & Cogan, E. (1996). Subacute mitochondrial liver disease in a patient with AIDS: possible relationship to prolonged fluconazole administration. *Am J Gastroenterol*, *91*(1), 165-168. https://www.ncbi.nlm.nih.gov/pubmed/8561126.

Gupta, A. K., & Shear, N. H. (1997). Terbinafine: an update. *J Am Acad Dermatol*, *37*(6), 979-988. https://doi.org/10.1016/s0190-9622(97)70076-8.

Gupta, A. K., Taborda, V. B. A., Taborda, P. R. O., Shemer, A., Summerbell, R. C., & Nakrieko, K. A. (2020). High prevalence of mixed infections in global onychomycosis. *PLoS One*, *15*(9), e0239648. https://doi.org/10.1371/journal.pone.0239648.

Hauben, M., & Aronson, J. K. (2009). Defining 'signal' and its subtypes in pharmacovigilance based on a systematic review of previous definitions. *Drug Saf*, *32*(2), 99-110. https://doi.org/10.2165/00002018-200932020-00003.

Hollier, L. M., & Cox, S. M. (1995). Fluconazole (Diflucan). *Infect Dis Obstet Gynecol*, *3*(6), 222-225. https://doi.org/10.1155/S1064744995000676.

Hosseini-Yeganeh, M., & McLachlan, A. J. (2002). Physiologically based pharmacokinetic model for terbinafine in rats and humans. *Antimicrob Agents Chemother*, *46*(7), 2219-2228. https://doi.org/10.1128/AAC.46.7.2219-2228.2002.

Hoy, S. M. (2022). Oteseconazole: First Approval. *Drugs*, *82*(9), 1017-1023. https://doi.org/10.1007/s40265-022-01734-y.

Humphrey, M. J., Jevons, S., & Tarbit, M. H. (1985). Pharmacokinetic evaluation of UK-49,858, a metabolically stable triazole antifungal drug, in animals and humans. *Antimicrob Agents Chemother*, *28*(5), 648-653. https://doi.org/10.1128/AAC.28.5.648.

Iorizzo, M., Piraccini, B. M., Rech, G., & Tosti, A. (2005). Treatment of onychomycosis with oral antifungal agents. *Expert Opin Drug Deliv*, *2*(3), 435-440. https://doi.org/10.1517/17425247.2.3.435.

Iorizzo, M., Piraccini, B. M., & Tosti, A. (2010). Today's treatments options for onychomycosis. *J Dtsch Dermatol Ges*, *8*(11), 875-879. https://doi.org/10.1111/j.1610-0387.2010.07499.x.

Jensen, J. C. (1989). Clinical pharmacokinetics of terbinafine (Lamisil). *Clin Exp Dermatol*, *14*(2), 110-113. https://doi.org/10.1111/j.1365-2230.1989.tb00904.x.

Jeong, I., Park, J. S., Cho, Y. J., Yoon, H. I., Song, J., Lee, C. T., & Lee, J. H. (2015). Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. *J Korean Med Sci*, *30*(2), 167-172. https://doi.org/10.3346/jkms.2015.30.2.167.

Jorda, T., & Puig, S. (2020). Regulation of Ergosterol Biosynthesis in Saccharomyces cerevisiae. *Genes (Basel)*, *11*(7). https://doi.org/10.3390/genes11070795.

Joseph-Horne, T., & Hollomon, D. W. (1997). Molecular mechanisms of azole resistance in fungi. *FEMS Microbiol Lett*, *149*(2), 141-149. https://doi.org/10.1111/j.1574-6968.1997.tb10321.x.

Khoza, S., Moyo, I., & Ncube, D. (2017). Comparative Hepatotoxicity of Fluconazole, Ketoconazole, Itraconazole, Terbinafine, and Griseofulvin in Rats. *J Toxicol*, *2017*, 6746989. https://doi.org/10.1155/2017/6746989.

Kreijkamp-Kaspers, S., Hawke, K., Guo, L., Kerin, G., Bell-Syer, S. E., Magin, P., Bell-Syer, S. V., & van Driel, M. L. (2017). Oral antifungal medication for toenail onychomycosis. *Cochrane Database Syst Rev*, *7*(7), CD010031. https://doi.org/10.1002/14651858.CD010031.pub2.

Krishnan-Natesan, S. (2009). Terbinafine: a pharmacological and clinical review. *Expert Opin Pharmacother*, *10*(16), 2723-2733. https://doi.org/10.1517/14656560903307462.

Lang, R., Stokes, W., Lemaire, J., Johnson, A., & Conly, J. (2019). A case report of Coccidioides posadasii meningoencephalitis in an immunocompetent host. BMC Infectious Diseases, 19(1), 722. https://doi.org/10.1186/s12879-019-4329-0.

Leyden, J. (1998). Pharmacokinetics and pharmacology of terbinafine and itraconazole. *J Am Acad Dermatol*, *38*(5 Pt 3), S42-47. https://doi.org/10.1016/s0190-9622(98)70483-9.

Lipner, S. R., & Scher, R. K. (2019a). Onychomycosis: Clinical overview and diagnosis. *J Am Acad Dermatol*, *80*(4), 835-851. https://doi.org/10.1016/j.jaad.2018.03.062.

Lipner, S. R., & Scher, R. K. (2019b). Onychomycosis: Treatment and prevention of recurrence. *J Am Acad Dermatol*, *80*(4), 853-867. https://doi.org/10.1016/j.jaad.2018.05.1260.

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Isoniazid. [Updated 2018 Apr 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548754/.

Ly, P., Subrt, A., & Wilkerson, M. (2019). Rhabdomyolysis attributed to terbinafine: A rare occurrence that can be mistaken for terbinafine-induced hepatotoxicity. *JAAD Case Rep*, *5*(1), 47-49. https://doi.org/10.1016/j.jdcr.2018.08.025.

Machard, B., Misslin, P., & Lemaire, M. (1989). Influence of plasma protein binding on the brain uptake of an antifungal agent, terbinafine, in rats. *J Pharm Pharmacol*, *41*(10), 700-704. https://doi.org/10.1111/j.2042-7158.1989.tb06344.x.

Manning, P. R., Lee, P. V., Denson, T. A., & Gilman, N. J. (1980). Determining educational needs in the physician's office. *JAMA*, *244*(10), 1112-1115. https://www.ncbi.nlm.nih.gov/pubmed/7411764.

MedDRA. (n.d.). https://www.meddra.org/sites/default/files/guidance/file/smq_intguide_21_0_english.pdf

Mikamo, H., Yin, X. H., Hayasaki, Y., Shimamura, Y., Uesugi, K., Fukayama, N., Satoh, M., & Tamaya, T. (2002). Penetration of ravuconazole, a new triazole antifungal, into rat tissues. *Chemotherapy*, *48*(1), 7-9. https://doi.org/10.1159/000048580.

Nanyonga, S. M., Kitutu, F. E., Kalyango, J., Frank, M., & Kiguba, R. (2022). High Burden of Adverse Drug Reactions to Isoniazid Preventive Therapy in People Living With HIV at 3 Tertiary Hospitals in Uganda: Associated Factors. *J Acquir Immune Defic Syndr*, *89*(2), 215-221. https://doi.org/10.1097/QAI.0000000000002842.

Pappas, P. G., Kauffman, C. A., Perfect, J., Johnson, P. C., McKinsey, D. S., Bamberger, D. M., Hamill, R., Sharkey, P. K., Chapman, S. W., & Sobel, J. D. (1995). Alopecia associated with fluconazole therapy. *Ann Intern Med*, *123*(5), 354-357. https://doi.org/10.7326/0003-4819-123-5-199509010-00006.

Patel, K., Roberts, J. A., Lipman, J., Tett, S. E., Deldot, M. E., & Kirkpatrick, C. M. (2011). Population pharmacokinetics of fluconazole in critically ill patients receiving

continuous venovenous hemodiafiltration: using Monte Carlo simulations to predict doses for specified pharmacodynamic targets. *Antimicrob Agents Chemother*, *55*(12), 5868-5873. https://doi.org/10.1128/AAC.00424-11.

Petraitiene, R., Petraitis, V., Lyman, C. A., Groll, A. H., Mickiene, D., Peter, J., Bacher, J., Roussillon, K., Hemmings, M., Armstrong, D., Avila, N. A., & Walsh, T. J. (2004). Efficacy, safety, and plasma pharmacokinetics of escalating dosages of intravenously administered ravuconazole lysine phosphoester for treatment of experimental pulmonary aspergillosis in persistently neutropenic rabbits. *Antimicrob Agents Chemother*, *48*(4), 1188-1196. https://doi.org/10.1128/AAC.48.4.1188-1196.2004.

Petranyi, G., Meingassner, J. G., & Mieth, H. (1987). Antifungal activity of the allylamine derivative terbinafine in vitro. *Antimicrob Agents Chemother*, *31*(9), 1365-1368. https://doi.org/10.1128/AAC.31.9.1365.

Pfaller, M. A., Messer, S. A., Hollis, R. J., Jones, R. N., & Group, S. P. (2002). Antifungal activities of posaconazole, ravuconazole, and voriconazole compared to those of itraconazole and amphotericin B against 239 clinical isolates of Aspergillus spp. and other filamentous fungi: report from SENTRY Antimicrobial Surveillance Program, 2000. *Antimicrob Agents Chemother*, *46*(4), 1032-1037. https://doi.org/10.1128/AAC.46.4.1032-1037.2002.

Pierson-Marchandise, M., Gras, V., Moragny, J., Micallef, J., Gaboriau, L., Picard, S., Choukroun, G., Masmoudi, K., Liabeuf, S., & French National Network of Pharmacovigilance, C. (2017). The drugs that mostly frequently induce acute kidney injury: a case - noncase study of a pharmacovigilance database. *Br J Clin Pharmacol*, *83*(6), 1341-1349. https://doi.org/10.1111/bcp.13216.

Roberts, D. T., Taylor, W. D., Boyle, J., & British Association of, D. (2003). Guidelines for treatment of onychomycosis. *Br J Dermatol*, *148*(3), 402-410. https://doi.org/10.1046/j.1365-2133.2003.05242.x.

Rosen, T., & Stein Gold, L. F. (2016). Antifungal Drugs for Onychomycosis: Efficacy, Safety, and Mechanisms of Action. *Semin Cutan Med Surg*, *35*(3 Suppl 3), S51-55. https://doi.org/10.12788/j.sder.2016.009.

Rothman, K. J., Lanes, S., & Sacks, S. T. (2004). The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf*, *13*(8), 519-523. https://doi.org/10.1002/pds.1001.

Russom, M., Debesai, M., Zeregabr, M., Berhane, A., Tekeste, T., & Teklesenbet, T. (2018). Serious hepatotoxicity following use of isoniazid preventive therapy in HIV patients in Eritrea. *Pharmacol Res Perspect*, *6*(4), e00423. https://doi.org/10.1002/prp2.423.

Scher, R. K., Breneman, D., Rich, P., Savin, R. C., Feingold, D. S., Konnikov, N., Shupack, J. L., Pinnell, S., Levine, N., Lowe, N. J., Aly, R., Odom, R. B., Greer, D. L., Morman, M. R., Bucko, A. D., Tschen, E. H., Elewski, B. E., & Smith, E. B. (1998). Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol*, *38*(6 Pt 2), S77-86. https://doi.org/10.1016/s0190-9622(98)70490-6.

Shin, J. H., Kook, H., Shin, D. H., Hwang, T. J., Kim, M., Suh, S. P., & Ryang, D. W. (2000). Nosocomial cluster of Candida lipolytica fungemia in pediatric patients. *Eur J Clin Microbiol Infect Dis*, *19*(5), 344-349. https://doi.org/10.1007/s100960050491.

Shirwaikar, A. A., Thomas, T., Shirwaikar, A., Lobo, R., & Prabhu, K. S. (2008). Treatment of onychomycosis: an update. *Indian J Pharm Sci*, *70*(6), 710-714. https://doi.org/10.4103/0250-474X.49088.

Sigurgeirsson, B., & Baran, R. (2014). The prevalence of onychomycosis in the global population: a literature study. *J Eur Acad Dermatol Venereol*, *28*(11), 1480-1491. https://doi.org/10.1111/jdv.12323.

Sigurgeirsson, B., Olafsson, J. H., Steinsson, J. B., Paul, C., Billstein, S., & Evans, E. G. (2002). Long-term effectiveness of treatment with terbinafine vs itraconazole in onychomycosis: a 5-year blinded prospective follow-up study. *Arch Dermatol*, *138*(3), 353-357. https://doi.org/10.1001/archderm.138.3.353.

Singal, A., & Khanna, D. (2011). Onychomycosis: Diagnosis and management. *Indian J Dermatol Venereol Leprol*, *77*(6), 659-672. https://doi.org/10.4103/0378-6323.86475.

Sobel, J. D., & Nyirjesy, P. (2021). Oteseconazole: an advance in treatment of recurrent vulvovaginal candidiasis. *Future Microbiol*, *16*, 1453-1461. https://doi.org/10.2217/fmb-2021-0173.

Somchit, N., Hassim, S. M., & Samsudin, S. H. (2002). Itraconazole- and fluconazole-induced toxicity in rat hepatocytes: a comparative in vitro study. *Hum Exp Toxicol*, *21*(1), 43-48. https://doi.org/10.1191/0960327102ht208oa.

Suvarna, V. (2010). Phase IV of Drug Development. *Perspect Clin Res*, *1*(2), 57-60. https://www.ncbi.nlm.nih.gov/pubmed/21829783.

Thomas, J., Jacobson, G. A., Narkowicz, C. K., Peterson, G. M., Burnet, H., & Sharpe, C. (2010). Toenail onychomycosis: an important global disease burden. *J Clin Pharm Ther*, *35*(5), 497-519. https://doi.org/10.1111/j.1365-2710.2009.01107.x.

Triggle, D. J., & Taylor, J. B. (2006). *Comprehensive Medicinal Chemistry II* (Vol. 8). Elsevier.

Unal Yuksekgonul, A., Ertugrul, I., & Karagoz, T. (2021). Fluconazole-associated QT interval prolongation and Torsades de Pointes in a paediatric patient. *Cardiol Young*, *31*(12), 2035-2037. https://doi.org/10.1017/S1047951121001992.

Vickers, A. E., Sinclair, J. R., Zollinger, M., Heitz, F., Glanzel, U., Johanson, L., & Fischer, V. (1999). Multiple cytochrome P-450s involved in the metabolism of terbinafine suggest a limited potential for drug-drug interactions. *Drug Metab Dispos*, *27*(9), 1029-1038. https://www.ncbi.nlm.nih.gov/pubmed/10460803.

Vora, D., Bharti, B., Solanki, P., Kothari, A., & Meher, K. (2014). A study to compare efficacy of various oral antifungals (Fluconazole, Terbinafine, Itraconazole) in treatment of Onychomycosis. *J Res Med Dent Sci*, *2*(4), 49.

Yamaguchi, H. (2016). Potential of Ravuconazole and its Prodrugs as the New Oral Therapeutics for Onychomycosis. *Med Mycol J*, *57*(4), E93-E110. https://doi.org/10.3314/mmj.16-00006.

Yan, J., Wang, X., & Chen, S. (2014). Systematic review of severe acute liver injury caused by terbinafine. *Int J Clin Pharm*, *36*(4), 679-683. https://doi.org/10.1007/s11096-014-9969-y.

Yan, J. H., Marino, M. R., Smith, R. A., Kanamaluru, V., O'Mara, E. M., & Grasela, D. M. (2006). The effect of ravuconazole on the pharmacokinetics of nelfinavir in healthy male volunteers. *J Clin Pharmacol*, *46*(2), 193-200. https://doi.org/10.1177/0091270005283462.

Zhou, S., & Bagga, A. (2020). Rhabdomyolysis and Acute Kidney Injury Associated With Terbinafine Use: A Case Report. *Can J Kidney Health Dis*, *7*, 2054358120951371. https://doi.org/10.1177/2054358120951371.