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Retrospective analysis of adverse events with systemic onychomycosis medications reported to the United States Food and Drug Administration

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\textbf{ABSTRACT}

\textbf{Background:} Onychomycosis is the most common nail condition and when left untreated, has esthetic, physical and emotional-social sequelae.  
\textbf{Objective:} To classify the most common adverse reactions with the oral onychomycosis medications terbinafine, itraconazole, and off-label fluconazole.  
\textbf{Methods:} The United States Food and Drug Administration Adverse Event Reporting (FAERS) database was analyzed for common adverse reactions with terbinafine, itraconazole, and off-label fluconazole. Transaminase elevations reported with terbinafine usage were further subdivided by the age group. Google Trends was used to examine public interest in these medications and compare yearly data with adverse events in the FAERS database.  
\textbf{Results:} The most common adverse reaction with terbinafine was taste disturbance and the most common adverse events with itraconazole and fluconazole were drug interactions. Transaminase elevations associated with terbinafine were extremely rare in the pediatric population. Increased Google searches for all three medications were also associated with increased reporting of adverse events in the FAERS database.  
\textbf{Conclusion:} Patients should be counseled that taste disturbance with terbinafine is the most common adverse event. Concomitant medications must be reviewed carefully before prescribing itraconazole or fluconazole since drug interactions are relatively common. Public interest in onychomycosis has increased in recent years, potentially explaining increased prescribing of oral onychomycosis medications and increased reporting to FAERS.

\textbf{Abbreviations:} FDA: Federal Drug Administration; FAERS: Federal Drug Administration Adverse Event Reporting System; LFT: Liver Function Test; US: United States

\textbf{Introduction}

Onychomycosis is the most common nail condition with a worldwide prevalence of 5.5\%. Appropriate treatment is important to relieve pain, paresthesias, and improve quality of life (1). The goal of onychomycosis treatment is to eliminate the fungal infection and restore the nail to its normal state. Therapy is individualized based on number or nails affected, nail thickness, nail plate surface area involved, infecting organism(s), patient co-morbidities, cost, and patient preferences. Onychomycosis therapies include oral antifungals, topical antifungals, and devices. Overall, oral systemic agents are associated with higher mycologic (negative potassium hydroxide microscopy and negative culture) and complete cure rates (mycologic cure and a clinically completely normal nail) and have shorter durations of treatment. Systemic onychomycosis medications approved by the United States (US) Federal Drug Administration (FDA) are griseofulvin, terbinafine, and itraconazole, with the latter two and off-label fluconazole prescribed most frequently (2,3). Therefore, our objectives were to determine the most commonly reported adverse events to the US FDA associated with these medications (4).

\textbf{Material and methods}

A retrospective study of adverse events with terbinafine, itraconazole, and fluconazole from 1 January 1993 to 30 June 2019 was performed using the Federal Drug Administration Adverse Event Reporting System (FAERS) Database. In FAERS, adverse events are classified by reaction terms. The 20 most commonly reported reaction terms for each of these medications were recorded.

To determine the prevalence of aminotransferase abnormalities in pediatric versus adult populations, increases in AST and ALT were analyzed by age. While overall prescribing data for all three of these medications was not available, we sought to compare yearly adverse events in the FAERS database with annual public interest for each of the three medications using the Google Trends search terms for terbinafine and Lamisil, fluconazole and Diflucan, and itraconazole and Sporanox. Google Trends data were downloaded from Google (5), analyzed for all available years 2004–2018, and compared to the yearly numbers of adverse events reported to the FDA for all three medications.

\textbf{Results}

The top 20 most commonly reported adverse events are listed in Table 1. For terbinafine (11,658 cases), ‘ageusia/dysgeusia’ (1490, 12\%), ‘AST/ALT elevations’ (762, 6\%), and ‘pruritus’ (718, 6\%) were most often reported. For itraconazole (9830 cases), ‘drug interactions’ (926, 9\%), ‘dermatitis’ (627, 6\%), and ‘pruritus’...
For fluconazole (18,714 cases), 'drug interactions' (1968, 11%), 'drug ineffective' (1549, 8%), and 'pyrexia' (913, 5%) were the most common.

AST/ALT elevations reported with terbinafine comprised a total of 762 cases: under 3 years (0, 0%), 3–11 years (3, 0.4%), 12–17 years (3, 0.4%), 18–64 years (462, 60.6%), 64–85 years (237, 31.1%), over 85 years (14, 1.8%), and unspecified age (43, 5.6%) (Figure 1).

Between 2010 and 2018, there was an increase in both the number of adverse events associated with terbinafine reported to FAERS and the Google Trends for terbinafine and Lamisil with an isolated dip in 2016 (Figure 2). There was a strong association between the number of cases reported to the FDA and the Google Trend search (Spearman-rank coefficient testing, $R = 0.8$ ($p < .001$).

From 2014 to 2018, there was an increase in both the number of adverse events with itraconazole reported to FAERS and the Google Trends for itraconazole and Sporanox with an isolated dip in 2016 for cases reported to FAERS (Figure 3). There was an association between the number of cases reported to the FDA and the Google Trend search (Spearman-rank coefficient testing, $R = 0.25$ ($p < .38$), however, it was not statistically significant.

Between 2008 and 2018, there was an increase in both the number of adverse events with fluconazole reported to FAERS and the Google Trends for fluconazole and Diflucan, with an isolated dip in the Google Trends in 2016 (Figure 4). There was a strong association between the number of cases reported to the FDA and the Google Trend search (Spearman-rank coefficient testing, $R = 0.94$ ($p < .001$).

**Discussion**

Using FAERS, we analyzed the adverse effects reported to the FDA with the most commonly prescribed oral medications for onychomycosis over a 26-year period. Our study indicates that while hepatotoxicity is an important safety concern associated with terbinafine, patients are twice as likely to experience taste loss/change. As per the package insert for terbinafine, taste disturbances typically resolve within weeks of discontinuing the medication (6). In a case series ($n = 6$), taste disturbances occurred 4–6 weeks after starting the medication, and resolved 6–8 weeks following discontinuation of the drug (7). In one case report, a patient experienced complete loss of taste after 6 weeks of taking terbinafine. The medication was stopped, but

| Table 1. The top 20 most common adverse events reported with terbinafine, itraconazole, and fluconazole in the FAERS database from 1 January 1993 to 30 June 2019. |
|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Terbinafine Case | Percent | Itraconazole Cases | Percent | Fluconazole Cases | Percent |
| Ageusia | 772 | 7 | Drug interaction | 926 | 9 | Drug interaction | 1968 | 11 |
| Pruritus | 718 | 6 | Dermatitis | 627 | 6 | Drug ineffective | 1549 | 8 |
| Dysgeusia | 563 | 5 | Pyrexia | 541 | 6 | Pyrexia | 913 | 5 |
| Pyrexia | 539 | 5 | Drug ineffective | 435 | 4 | Nausea | 658 | 4 |
| Drug ineffective | 499 | 4 | Drug ineffective | 406 | 4 | Condition aggravated | 600 | 3 |
| Rash | 473 | 4 | Dyspnea | 383 | 4 | Diarrhea | 580 | 3 |
| Condition aggravated | 469 | 4 | Edema peripheral | 326 | 3 | Vomiting | 524 | 3 |
| Nausea | 466 | 4 | Nausea | 317 | 3 | Pruritus | 511 | 3 |
| Weight decreased | 453 | 4 | Hepatic function abnormal | 314 | 3 | Drug hypersensitivity | 505 | 3 |
| Pyrexia | 452 | 4 | Condition aggravated | 298 | 3 | Fungal infection | 502 | 3 |
| Urticaria | 413 | 4 | Asthenia | 271 | 3 | Acute kidney injury | 494 | 3 |
| Urticaria | 396 | 3 | Asthenia | 265 | 3 | Thrombocytopenia | 477 | 3 |
| Malaise | 393 | 3 | Rash Maculo-Papular | 257 | 3 | Headache | 460 | 2 |
| Decreased appetite | 384 | 3 | Headache | 248 | 3 | Dyspnea | 455 | 2 |
| Aspartate aminotransferase increased | 383 | 3 | Vomiting | 233 | 2 | Candida infection | 447 | 2 |
| Alanine aminotransferase increased | 379 | 3 | Abdominal pain | 205 | 2 | Pneumonia | 437 | 2 |
| Drug interaction | 361 | 3 | Dizziness | 202 | 2 | Rash | 431 | 2 |
| Fatigue | 351 | 3 | Thrombocytopenia | 202 | 2 | Sepsis | 411 | 2 |
| Headache | 342 | 3 | Diarrhea | 200 | 2 | Dermatitis | 411 | 2 |
| Diarrhea | 297 | 3 | Fatigue | 192 | 2 | Asthenia | 397 | 2 |
corresponding behavioral sensitivity appear to decrease with age. In animal studies, NaCl neural-response magnitude and lower BMIs experiences higher rates of taste disturbances. In lipophilic (11). This lipophilicity might explain why patients with higher BMIs experiences higher rates of taste disturbances. In lipophilic (11). This lipophilicity might explain why patients with higher BMIs experiences higher rates of taste disturbances. In lipophilic (11). This lipophilicity might explain why patients with higher BMIs experiences higher rates of taste disturbances.

Pediatric onychomycosis clinical trials with terbinafine have not been performed, but it is prescribed off-label to this population for this indication (13). In the FAERS database, no AST or ALT elevations with terbinafine were reported for children under 3 years of age, while for patients 3 to 17 years old, there have been only six cases of AST or ALT elevations reported, and 462 cases were reported for patients ages 18–64 years. Therefore, hepatotoxic side effects with terbinafine are exceedingly rare in children.

Our data are consistent with the previous literature, in which in a pooled analysis of 84 children under the age of 18, there was only 1 (1.2%) reported event of transaminase elevation (14). Another study of 144 pediatric patients who underwent laboratory monitoring of liver function panels and/or complete blood cell counts while taking terbinafine for onychomycosis further supports that liver injury with terbinafine is exceedingly rare. Laboratory monitoring was performed prior to treatment (34 patients, 23.6%) or prior to treatment and at 6 weeks (102 patients, 70.8%). Out of the 144 patients, only 6 (4.2%) had mild transaminase abnormalities, and all resolved with discontinuation of the medication (15). Our study also compared the rate of liver toxicity in children and adults, showing that in FAERS, patients 18–64 years old were 77 times more likely to report liver enzyme elevations than patients 3–17 years old. Therefore, interval laboratory monitoring may not be necessary for children under 18 years old, reducing the overall cost of treatment.

Terbinafine is an inexpensive generic drug, with a monthly cost of $7.19 when obtained through major retailers in the US (16). The cost of a single serum AST and ALT is $5.75 and $5.81, respectively, determined by the 2019 clinical laboratory fee schedule by the Centers for Medicare & Medicaid Services (17), and the cost of venipuncture is $18 (18). Stolmeier et al. concluded that 417 ALT measurements would have been drawn in patients taking terbinafine to identify one actionable ALT measurement. The mean age of patients in this study was 42.8 years (19). Therefore, the FAERS data combined with the previously published reports suggests that interval laboratory monitoring is unnecessary in healthy adults. However, since the FAERS data showed the AST/ALT elevation accounted for 6% of adverse effects with terbinafine, it may be reasonable to perform interval laboratory monitoring for adults with other risk factors for hepatotoxicity. Patients should also be educated to watch for signs of liver damage including a mildly tender liver, dark urine, and jaundice, as these symptoms may appear even before the serum markers peak (20).

For itraconazole, the most common adverse reaction found in FAERS was interactions with other medications. Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of CYP3A4. Therefore, itraconazole can lead to increased concentrations of medications that are also metabolized via CYP3A4 due to decreased metabolism of those drugs (21). Some examples of medications that can be life threatening when taken with itraconazole are the class IA antiarrhythmic quinidine and class III antiarrhythmic dofetilide, whose combination can cause QT prolongation. When itraconazole is taken with the benzodiazepines, alprazolam, diazepam, oral midazolam, and triazolam, their concentrations are increased, leading to sedation. Commonly prescribed medications including the HMG CoA-Reductase inhibitors atorvastatin, cerivastatin, lovastatin, and simvastatin, when taken along with itraconazole can cause rhabdomyolysis due to increased concentrations of the HMG COA-reductase (21). Therefore, based on our findings that drug interactions with

![Figure 3](image3.png) **Figure 3.** Number of adverse events with itraconazole in the FAERS database by year (1993–2018) plotted with Google Trends search terms for the search terms itraconazole and Sporanox by year (2004–2018). Google Trends data prior to 2004 were not available. Google Trend Interest Points are defined by how frequently a given search term is entered into Google’s search engine relative to the site’s total search volume over a given period of time.

![Figure 4](image4.png) **Figure 4.** Number of adverse events with fluconazole in the FAERS database by year (1993–2018) plotted with Google Trends search terms for the search terms fluconazole and Diflucan (2004–2018). Google Trends data prior to 2004 were not available. Google Trend Interest Points are defined by how frequently a given search term is entered into Google’s search engine relative to the site’s total search volume over a given period of time.
itraconazole are relatively common in FAERS, it is paramount for physicians to review concomitant medications before prescribing itraconazole. It is equally important for physicians to be aware that patients are taking itraconazole and to check medication interactions before prescribing other medications.

Like itraconazole, the most common adverse event in FAERS for fluconazole was also drug interactions. Some medications that interact with fluconazole are the sulfonylurea oral hypoglycemic agents: tolbutamide, glipizide, and glyburide. Fluconazole can increase their concentration, leading to hypoglycemic episodes (22). Another interaction is with warfarin. In one study of 13 patients taking fluconazole and warfarin, the prothrombin time was increased by a mean of 7% for 12 patients, with one patient experiencing a doubling in prothrombin time (22). Therefore, as with itraconazole, it is important for physicians to thoroughly review current medications before prescribing fluconazole.

The Google Trends searches for all three medications and the number of cases reported to FAERS increased in the period following 2014. Efinaconazole (Jublia) was approved by the FDA on 6 June 2014 (23). An aggressive marketing campaign followed with print and television advertisements in 2014 and 2015 (24). This may have led to increased public interest in onychomycosis, as evidenced by the Google Trends curves for the three oral antifungals, and prescribing by physicians, shown by the number of cases reported to FAERS after 2014 for all three medications. Therefore, understanding potential adverse events associated with these antifungals has become more significant. Our study also shows that pharmaceutical companies can have a direct impact on public awareness of a medical condition and prescribing patterns through direct to consumer marketing.

Limitations of this study include its retrospective design, lack of FAERS data prior to January 1993, and lack of overall prescribing data for terbinafine, itraconazole, and fluconazole. In addition, because data in FAERS are reported by patients, health care providers, and pharmaceutical companies, these adverse effects have not been confirmed by other means.

For future studies, it would be important to analyze if multiple courses of terbinafine increase hepatotoxicity, since recurrences are common (2). It is also imperative to quantitate overall US prescription data to better understand the relative frequency of these adverse effects reported to the FDA. In addition, most clinical trials with terbinafine exclude patients with preexisting liver disease, so there are no data on utilizing terbinafine in these patients. Therefore, it is essential to understand whether terbinafine can be given to these patients if followed closely, in light of the few efficacious options available to these patients.

In conclusion, our study indicates that while hepatotoxicity is an important safety concern associated with terbinafine, patients are far more likely to experience taste loss/change. In addition, ALT/AST elevations associated with terbinafine are relatively uncommon in adults and are exceedingly rare in children. Since drug interactions are the most common adverse reactions associated with itraconazole and itraconazole, it is essential to review concomitant medications prior to prescribing for onychomycosis.

Disclosure statement
Yu Wang and Dr Lipner have no conflicts of interest relevant to the content of the submission. This work has not been previously published.

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