Journal of Dermatological Treatment

ISSN: 0954-6634 (Print) 1471-1753 (Online) Journal homepage: https://www.tandfonline.com/loi/ijdt20

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

Yu Wang & Shari R. Lipner

To cite this article: Yu Wang & Shari R. Lipner (2020): Retrospective analysis of adverse events with systemic onychomycosis medications reported to the United States Food and Drug Administration, Journal of Dermatological Treatment, DOI: 10.1080/09546634.2019.1708242

To link to this article: https://doi.org/10.1080/09546634.2019.1708242

Accepted author version posted online: 21 Dec 2019.
Published online: 06 Jan 2020.

JOURNAL OF DERMATOLOGICAL TREATMENT
https://doi.org/10.1080/09546634.2019.1708242

Taylor & Francis
Taylor & Francis Group

ARTICLE

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

Yu Wang[a] and Shari R. Lipner[b]

[a]SUNY Stonybrook Medical School, Stonybrook, NY, USA; [b]Department of Dermatology, Weill Cornell Medicine, New York, NY, USA

ABSTRACT

Background: Onychomycosis is the most common nail condition and when left untreated, has esthetic, physical and emotional-social sequelae.

Objective: To classify the most common adverse reactions with the oral onychomycosis medications terbinafine, itraconazole, and off-label fluconazole.

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.

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.

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.

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

ARTICLE HISTORY
Received 24 October 2019
Accepted 19 December 2019

KEYWORDS
Onychomycosis; fungal nail infection; FDA; FAERS; adverse events; liver toxicity; terbinafine; fluconazole; itraconazole; taste disturbance; AST; ALT; drug interaction; Google; Google Trends

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).

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.

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'

CONTACT Shari R. Lipner shl9032@med.cornell.edu Department of Dermatology, Weill Cornell Medicine, 1305 York Avenue, New York, NY 10021, USA.

Table 1. The top 20 most commonly reported 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	Pruritus	541	6	Pyrexia	913	5
Therapeutic product effect decreased	539	5	Pyrexia	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	432	4	Condition aggravated	298	3	Fungal infection	502	3
Urticaria	413	4	Asthenia	271	3	Acute kidney Injury	494	3
Dermatitis	396	3	Urticaria	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

(541, 6%) were most frequent. 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 Trends 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, $R = 0.94$ ($p < .001$).

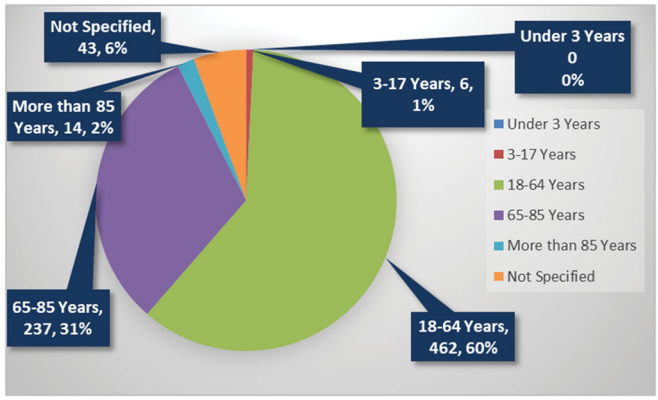

Figure 1. Number of cases of AST/ALT elevations in the FAERS database with terbinafine by age group (1 January 1993 to 30 June 2019).

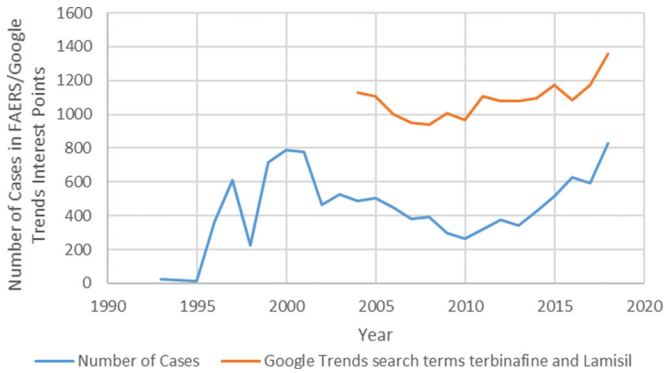

Figure 2. Number of adverse events with terbinafine in the FAERS database by year (1993–2018) plotted with Google Trends interest points for the search terms terbinafine and Lamisil by year (2004–2018). Google Trends data prior to 2004 were not available. Google Trend Interest Points are defined by how 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.

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

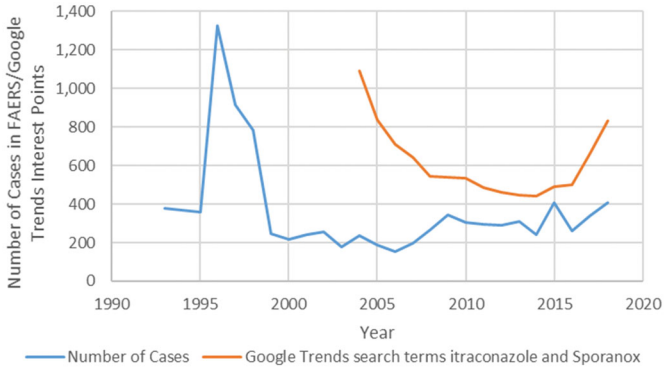

Figure 3. Number of adverse events with itraconazole in the FAERS database by year (1993–2018) plotted with Google Trends interest points for the search terms itraconazole and Sporanox by year (2004–2018). Google Trends data prior to 2004 were not available. Google Trend Interest Points are defined by 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.

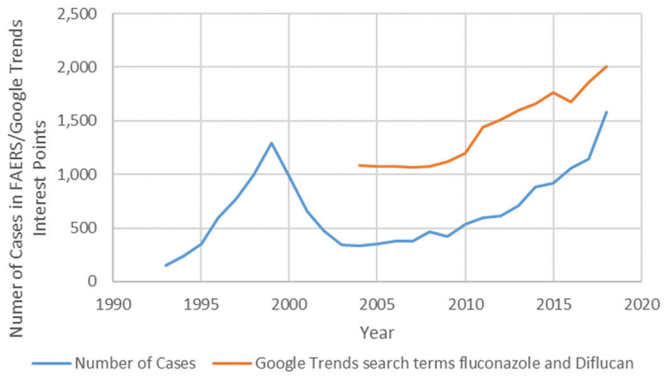

Figure 4. Number of adverse events with fluconazole in the FAERS database by year (1993–2018) plotted with Google Trends interest points for the search terms fluconazole and Diflucan (2004–2018). Google Trends data prior to 2004 were not available. Google Trend Interest Points are defined by how frequently 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.

three years later, the patient was still unable to taste sugar and salt (8). In one study that quantitatively assessed the taste function of six patients reporting taste disturbances with terbinafine, sour (citric acid) and bitter (caffeine) taste was more severely altered than sweet (sucrose) and salty (sodium chloride) taste compared to normal controls (9). Older patients and patients with lower BMI are more likely to experience taste disturbances with terbinafine. For example, in a study of 87 patients with self-reported taste loss following terbinafine and 362 controls who had taken terbinafine without this side effect, those with an BMI of 21 were 4 times more likely to develop taste disturbances when compared to patients with a BMI of 27 and greater (10). In addition, patients 55 years old and older were 4–5 times more likely to experience taste loss compared to patients 35 and younger (10). In a study involving 12 healthy volunteers who were given a 28-d course of terbinafine, the concentration was the highest in sebum compared to the stratum corneum and nail plate, demonstrating that the drug is lipophilic (11). This lipophilicity might explain why patients with lower BMIs experiences higher rates of taste disturbances. In addition, in animal studies NaCl neural-response magnitude and corresponding behavioral sensitivity appear to decrease with age (12).

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 years 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

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 marking 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.

References

1. Lipner SR, Scher RK. Onychomycosis: clinical overview and diagnosis. J Am Acad Dermatol. 2019;80:835–851.
2. Lipner SR, Scher RK. Onychomycosis: treatment and prevention of recurrence. J Am Acad Dermatol. 2019;80:853–867.
3. Lipner SR. Pharmacotherapy for onychomycosis: new and emerging treatments. Expert Opin Pharmacother. 2019;20:725–735.
4. Federal Drug Administration. 2019. Federal Drug Administration Adverse Event Reporting System [database]. Available from: https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis
5. Google. 2019. Google Trend [database]. Available from: https://trends.google.com/trends/?geo=US
6. LAMISIL (terbinafine hydrochloride) tablets [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; [accessed 2019 Sep 25]. Available from: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/Lamisil_tablets.pdf
7. Beutler M, Hartmann K, Kuhn M, et al. Taste disorders and terbinafine. BMJ. 1993;307:26.
8. Bong JL, Lucke TW, Evans CD. Persistent impairment of taste resulting from terbinafine. Br J Dermatol. 1998;139:747–748.
9. Doty RL, Haxel BR. Objective assessment of terbinafine-induced taste loss. Laryngoscope. 2005;115:2035–2037.
10. Stricker BHC, VAN Riemsdijk MM, Sturkenboom MCJM, et al. Taste loss to terbinafine: a case-control study of potential risk factors. Br J Clin Pharmacol. 2003;42:313–318.
11. Faergemann J, Zehender H, Denouël J, et al. Levels of terbinafine in plasma, stratum corneum, dermis-epidermis (without stratum corneum), sebum, hair and nails during and after 250 mg terbinafine orally once per day for four weeks. Acta Derm Venereol. 1993;73:305–309.
12. Granger EM, Glendinning JI, Smith JC, et al. Behavioral and electrophysiological responses to NaCl in young and old fischer-344 rats. Chem Senses. 1993;18:419–426.
13. Gupta AK, Chang P, Del Rosso JQ, et al. Onychomycosis in children: prevalence and management. Pediatr Dermatol. 1998;15:464–471.
14. Gupta AK, Mays RR, Versteeg SG, et al. Onychomycosis in children: safety and efficacy of antifungal agents. Pediatr Dermatol. 2018;35:552–559.
15. Patel D, Castelo-Soccio LA, Rubin AI, et al. Laboratory monitoring during systemic terbinafine therapy for pediatric onychomycosis. JAMA Dermatol. 2017;153:1326–1327.
16. Walmart, Inc. Retail prescription program drug list; 2019 [accessed 2019 Oct 2]. Available from: https://www.goodrx.com/spironolactone?label_override=spironolactone&form=tablet&dosage=100mg&quantity=30
17. Centers for Medicare & Medicaid Services. Clinical laboratory fee schedule. 2019 [accessed 2019 Oct 2]. Available from: https://www.cms.gov/apps/ama/license.asp?file=/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Downloads/19CLABQ1.zip
18. Centers for Medicare & Medicaid Services. Medicare provider utilization and payment data. 2017 [accessed 2019 Oct 2]. Available from: https://data.cms.gov/Medicare-Physician-Supplier/Medicare-Provider-Utilization-and-Payment-Data-Phy/fs4p-t5eq/data

19. Stolmeier DA, Stratman HB, McIntee TJ, et al. Utility of laboratory test result monitoring in patients taking oral terbinafine or griseofulvin for dermatophyte infections. JAMA Dermatol. 2018;154:1409–1416.
20. Lazaros GA, Papatheodoridis GV, Delladetsima JK, et al. Terbinafine-induced cholestatic liver disease. J Hepatol. 1996;24:753–756.
21. Food and Drug Administration. Aldactone SPORANOX® (itraconazole) Capsules. Physician Labeling. [accessed 2019 Oct 2]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020083s040s041s044lbl.pdf
22. Food and Drug Administration. DIFLUCAN® (fluconazole) Tablets. Physician Labeling. [accessed 2019 Oct 2]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019949s051lbl.pdf
23. Food and Drug Administration. Jublia (efinaconazole) approval date. [accessed 2019 Oct 2]. Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshot-jublia-efinaconazole
24. Sinclair N. 2016. Tv Ad Revenue Rising Pharmaceuticals Drugs. Available from: https://finance.yahoo.com/news/tv-ad-revenue-rising-pharmaceuticals-drugs-175632922.html