Title: Influence of drug class and healthcare setting on systemic antifungal expenditures in the United States from 2005-2015

Abstract

Purpose:

The incidence of invasive fungal infections and the availability of safer antifungals have increased in the last 20 years. However, few studies have comprehensively evaluated systemic antifungal use or expenditures in the U.S. We assessed overall and specific class trends in antifungal expenditures in various U.S. healthcare settings from 2005-2015.

Methods:

Systemic antifungal expenditures between 1/1/2005-12/31/2015 were obtained from the QuintilesIMS National Sales Perspective database, which provides a statistically valid projection of medication purchases from multiple markets throughout the U.S. Expenditures were described overall and by year, class, and healthcare setting. Trends were assessed using simple linear regression.

Results:

Overall expenditures for the 10-year period were $9.37 billion. The greatest proportion of expenditures occurred in non-federal hospitals (47.2%) and for the triazole class (57.6%). Between 2005-2015, total expenditures decreased from $1.1 billion to $894 million (-18.8%, $p=0.09$); however, expenditures in clinics and retail pharmacies increased (202%, $p<0.01$ and 13.8%, $p=0.04$, respectively), a trend most pronounced after 2012. Expenditures for flucytosine also increased (968.1%, $p<0.01$), particularly in clinics where there was a dramatic 6,640.9% increase ($p<0.01$).

Conclusions:

Despite overall decreases in systemic antifungal expenditures over the past 10 years, there were increased expenditures in clinics and retail pharmacies. Additional studies need to assess the indications for and appropriateness of antifungal use in these outpatient settings. Startlingly large increases in flucytosine expenditures were observed, particularly in the community. Further monitoring of both price and expenditures for this agent is warranted to ensure continued access to this potentially life-saving drug.

Keywords: antifungal, prescribing practices, expenditures

Introduction

Antimicrobial resistance has become a global public health crisis. A recent comprehensive report commissioned by the Wellcome Trust and the U.K. Department of Health estimated that, if left unchecked, antimicrobial resistance could result in an estimated 10 million deaths annually and a cumulative global cost of $100 trillion by 2050.[1] Much emphasis has been placed on curbing antibiotic use in both community and hospital settings to decrease antimicrobial resistance and toxic side effects, primarily with initiatives to decrease inappropriate antimicrobial use through antimicrobial stewardship programs (ASPs).[2-4] Inappropriate antifungal use also contributes to antimicrobial resistance with concomitant increased morbidity and mortality from infections with resistant fungi and unnecessary toxicity from antifungal medications.[8, 9] The incidence of invasive fungal infections, long felt to be problematic only in immunocompromised or oncology patients, has been increasing over the past 20 years,[10] with *Candida* now the most common cause of healthcare-associated bloodstream infections in many U.S. hospitals.[11] Estimates of the proportion of inpatient systemic antifungal use that is inappropriate are scarce and variable, ranging from 13% to 70%.[13-15] While there have been few studies that specifically evaluated the impact of decreasing inappropriate antifungal use, most have reported cost containment or cost savings and decreased antifungal resistance without a significant impact on clinical outcomes.[13, 18] As a result, attentions are now increasingly focused on antifungal use, costs, expenditures, and stewardship.[5]

Systemic anti-infectives were one of the top 3 categories of drug expenditures in nonfederal hospitals in 2014 and 2015.[19, 20] A significant proportion of antibiotic expenditures occur in the

outpatient and community setting, [19] and systemic antifungal expenditures may also vary by health care setting. Empirical and prophylactic therapy accounts for the majority of inpatient antifungal use;[13, 22-24] however, no studies have comprehensively evaluated systemic antifungal use in outpatient or community settings. Identifying specific antifungal classes and healthcare settings for which expenditures are increasing can help direct future studies aimed at developing targeted high-impact antifungal stewardship interventions. Furthermore, the financial effect of increased use of newer and more expensive antifungals with fewer side effects, such as triazoles and echinocandins, has yet to be explored; neither has the impact of recent dramatic price increases for older drugs such as flucytosine.[22] In this study, we assessed overall trends as well as specific class and agent trends in antifungal expenditures in various U.S. healthcare settings between 2005 and 2015.

Methods

Study design and setting:

This was a retrospective study of systemic antifungal expenditures in the U.S. from January 1, 2005 through December 31, 2015. Antifungal expenditures data were extracted from the QuintilesIMS National Sales Perspective (NSP) database.[23] The NSP captures 70% of all prescription medication purchases, with data then extrapolated to a statistically valid projection of 99% of all prescription medication purchases in U.S. Although this database provides a population-level view of drug expenditures, it does not provide information on utilization or number of prescriptions filled. Non-systemic antifungal medications (e.g., topical nystatin,

terbinafine, and ketoconazole) were excluded because we wanted to focus on expenditures for systemic oral and intravenously administered antifungals. Antifungals were stratified into class (polyenes, triazoles, flucytosine, and echinocandins) according to the QuintilesIMS Uniform System of Classification.[24] All antifungal agents in each class were approved by the Food and Drug Administration prior to 12/31/2006, except for isavuconazole, a triazole antifungal approved by the FDA in March 2015.

Healthcare settings:

Expenditures from retail community pharmacies, mail service pharmacies, clinics, non-federal hospitals, and 'other non-retail' pharmacies were included. Retail pharmacies were varied and included standalone chain and independent stores, mass merchandisers, and food and/or convenience stores with a licensed pharmacy. Mail service pharmacies were licensed mail order pharmacies affiliated with either private sector or federal facilities. Clinic expenditures included medications administered directly in the clinic and encompassed primary care and specialty physician offices and urgent care centers. Non-federal hospitals included licensed inpatient, specialty care, and rehabilitation hospitals that are not federally owned. 'Other non-retail' included federal facilities (e.g., Public Health Service and other federal hospitals and U.S. ships at sea) and other non-hospital facilities, such as long-term care facilities. Of note, beginning in 2014, QuintilesIMS did not include data from the Veterans Affairs (VA) healthcare system.

Statistical analysis:

Summary data for total antifungal expenditures over the entire period are reported, as is growth or the percentage change in expenditures from one year to the next. Expenditures were also

assessed specifically by year, class, and health care setting. Data were adjusted for inflation using the Consumer Price Index from the U.S. Department of Labor, Bureau for Labor Statistics (www.bls.gov), with all expenditures reported in 2015 dollars. Expenditure trends over the study period were assessed using simple linear trend regression models with a p-value of <0.05 considered statistically significant. Stata version 14 (StataCorp, Texas) was used for statistical analysis.

Results

Overall expenditures for antifungals in all care settings for the 10-year study period were $9.37 billion. Table 1 shows annual total expenditures and annual expenditures stratified by healthcare setting. Table 1 also shows growth in expenditures (both overall and stratified by healthcare setting) over the 10-year study. As expected, the greatest percentage of antifungal expenditures occurred in non-federal hospitals, which accounted for almost half of all expenditures ($4.4 billion; 47.2%). This was followed by retail (29.1%), other non-retail (13.3%), clinics (6.2%), and mail order pharmacies (4.3%). Overall, annual total antifungal expenditures decreased each year from 2005-2008, remained relatively constant until 2013 and then increased slightly in 2014 and 2015. This represented an overall 18.8% decrease from $1.1 billion to $894 million between 2005 and 2015 that was not statistically significant ($p=0.09$). While expenditures in non-federal hospitals significantly decreased (-46.5, $p<0.01$), expenditures in clinics and retail pharmacies significantly increased (202%, $p<0.01$ and 13.8%, $p=0.04$, respectively).

There was also significant variability in antifungal expenditures by class. Overall, triazoles accounted for the greatest proportion of expenditures ($5.4 billion; 57.6% of overall total expenditures), followed by echinocandins ($2.4 billion; 26.4%), polyenes ($1.3 billion; 14.1%) and flucytosine ($181 million; 1.9%). Between 2005-2015, significant decreases were observed for expenditures for echinocandins (-59%; $p<0.01$) and polyenes (-38.6%; $p<0.01$), while expenditures for triazoles increased by 10.8% ($p=0.03$) and for flucytosine by 968.2% ($p<0.01$) (Figure 1). Even more pronounced were trends in the annual growth (% change) in expenditures for each study year stratified by class (Figure 2). There was steadily increasing growth in annual flucytosine expenditures each year from 2005-2010 followed by stabilization until 2014-2015 when there was a 126.1% increase (Figure 2).

We next performed a more detailed analysis of antifungal expenditures for specific classes stratified by healthcare setting. Figure 3 demonstrates how healthcare setting influenced antifungal expenditures differentially by class. Retail and mail order settings were dominated by triazole expenditures (97.4% and 95.3% of expenditures, respectively). Triazoles also comprised the greatest proportion of expenditures in clinics (64.1%), although echinocandins (18.8%) and polyenes (14.0%) made substantial contributions. Non-federal hospital and other non-retail settings encompassed a mix of expenditures for all classes. Because clinic expenditures increased by the greatest proportion during the 10-year study, we chose to perform an additional analysis of expenditures by class within the clinic setting. Clinic expenditures for each antifungal class significantly increased over the study, and this trend was most pronounced after 2012 (Table 2). Flucytosine experienced widely fluctuating annual expenditure changes in clinics, with a rapid increase in expenditures from 2007-2009, a rapid decline from 2010-2012, and another rapid

increase from 2012-2015. Overall, there was a dramatic 6,640.9% increase in flucytosine expenditures in the clinic setting from 2005-2015 (Table 2).

Discussion:

In 2014, systemic antimicrobials were one of the top categories of drug expenditures in nonfederal hospitals.[19] Antifungals have historically lagged behind antibacterial and antiviral drugs in overall expenditures;[28] however, in the past decade, antifungals have garnered increasing attention as both the incidence of invasive fungal infections (IFIs) and the number of available drug classes and agents to treat IFIs has increased.[29-32] Furthermore, with the availability of newer antifungal agents with more favorable side effect profiles, there has been an increased emphasis on empiric antifungal use. For hospitals in particular, the clinical and economic burden of preventing and treating IFIs is high due to excess mortality, length of stay, and costs related to IFIs.[33, 34] Despite this increasing attention to IFIs and antifungal use, few large-scale studies of systemic antifungal expenditures have been performed, and most were conducted outside the U.S. or focused only on hospitalized patients.[22, 35-37]

In this study, we analyzed systemic antifungal expenditures from all healthcare settings in the U.S. and observed a non-significant trend toward decreased expenditures over the 10-year period. Overall expenditures may have decreased due to increased generic availability of frequently used expensive brand agents such as voriconazole and echinocandins or because of antimicrobial stewardship programs that promote judicious use of antifungals.[13] It is important to

note that, after expenditures decreased and then remained constant from 2005-2013, they began to increase again in 2014 and 2015. This may represent the beginning of an upward trend in systemic antifungal expenditures that may be related to recent price increases for antifungals (e.g., flucytosine) and/or increased use of more expensive antifungal agents (e.g. posaconazole). As an example of the latter, clinical guidelines now recommend posaconazole over other agents for primary prophylaxis of invasive mold infections in certain high-risk patient groups.[38] Only prior study has evaluated U.S. antifungal expenditures on an equivalent scale as our study. Desai et al. examined Medicaid data for systemic and topical antifungals between 1991 and 2009 and found that utilization remained constant but antifungal expenditures increased from $93.87 million to $143.76 million.[39] The difference in these results from our study may be related to the inclusion of topical antifungal agents (which accounted for the majority of prescriptions), the exclusive focus on the Medicaid population, and an earlier time period.

Furthermore, we observed interesting trends in antifungal expenditures by care setting and class. Substantial growth occurred in expenditures in the community setting, with clinic expenditures increasing by 202% from 2005 to 2015. Much of this growth was in expenditures for echinocandins and polyenes, both of which are classes administered intravenously. This may suggest a growing trend in outpatient parenteral antifungal therapy administered outside of hospital settings, such as in hematology-oncology or infectious diseases clinics with associated infusion centers. Furthermore, as expected, triazoles represented the greatest proportion of expenditures overall and in each study year, a finding similar to prior studies conducted outside the U.S.[35-37] Isavuconazole, the newest triazole, received FDA approval in March 2015 and appears poised to have a significant impact on the treatment of IFI.[29] In our study, expenditures

for isavuconazole totaled $11.9 million in 2015, or 2.08% of total triazole expenditures. Future studies should focus on assessment of the impact of this new agent on antifungal expenditures in various healthcare settings. Finally, one prior study by Garey et al. found increased echinocandin use in U.S. hospitals during the study period,[14] we observed decreased total expenditures for echinocandins in every setting except clinics. The discordant results may be related to the fact that we included more diverse care settings (not just hospitals) and a longer time period (10 years vs. 4 years for the Garey et al. study).

Perhaps the most striking class-specific expenditures trend in this study was for flucytosine. Clinic expenditures for this drug increased by a staggering 6,641%. Flucytosine is a pyrimidine analogue introduced in 1973 that is used infrequently but is a key component of treatment for Cryptococcal disease.[31] Since 2009, the U.S. price of flucytosine has steadily increased, with a 306% increase observed in the last 2 years and a now nearly 100-fold higher price in the U.S compared to Europe.[22] As of January 2016, there was only one FDA-approved pharmaceutical supplier of flucytosine, Valeant Pharmaceuticals.[22] Because the incidence of Cryptococcal disease has decreased in the U.S.,[42] utilization of flucytosine has likely decreased or at least remained constant; thus, the increase we observed in flucytosine expenditures in our study is likely the direct result of price increases. Although expenditures for flucytosine remained only a small proportion of total antifungal expenditures in our study, the dramatic increase in expenditures we observed raises concern for greater issues of access to antimicrobials and appropriate pharmaceutical pricing for older generic drugs.[22]

This study had a number of limitations. Expenditure data may not represent utilization or actual consumption of antifungal agents. Prior studies have demonstrated good correlation between antimicrobial purchasing data and dispensing data for hospital settings[36]; however, we were not able to draw conclusions regarding utilization or consumption based on our analysis. Furthermore, our dataset did not capture expenditures for systemic antifungals acquired without a prescription, although we anticipate that nonprescription use of systemic antifungals is likely to be low in the U.S. Finally, for 2014 and 2015, QuintilesIMS did not include expenditures from the VA healthcare system, which may have led to an underestimation of expenditures for those years in other, non-retail settings.

Despite these limitations, this study provides a comprehensive, national assessment of trends in antifungal expenditures for the past 10 years that we feel is highly valuable to those involved in public health, pharmacy, hospital administration, and antimicrobial stewardship. Although we identified an overall decrease in total antifungal expenditures, expenditures in the community setting increased substantially, as did expenditures for specific agents (e.g., flucytosine). This suggests a need for further studies on the indications for and appropriateness of antifungal prescribing in community settings to develop strategies to promote judicious and cost-effective antifungal use, particularly for parenteral antifungals.

Key points:

1. Between 2005-2015, despite an overall decrease in total antifungal expenditures in the U.S., an increase in expenditures was observed in community settings.
2. Antifungal expenditures for specific agents (e.g., flucytosine) also dramatically increased, particularly in community settings.
3. Increased attention should be paid to utilization of and expenditures for antifungal agents in outpatient clinics and retail pharmacies, perhaps through structured ambulatory care antimicrobial stewardship programs.

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365

366 **Keywords**: antifungal agents, prescription drugs, health expenditures

Figure captions:

Figure 1. Total antifungal expenditures (in $ millions) for each study year stratified by drug class. Percent of total expenditures for each class in each study year are indicated by the numbers on the bars.

Figure 2. Percent **change** in antifungal expenditures for each study year stratified by drug class.

Figure 3. Antifungal expenditures for each drug class as a percent of overall total antifungal expenditures in each healthcare setting for the 10-year study period.

Table 1. Trends in antifungal expenditures by healthcare setting and year

	Expenditures in $ millions (%)[a]												
Care setting	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total, 2005-2015	% Growth, 2005-2015
Non-federal hospital	616.1 (56.0)[b]	548.6 (57.0)	452.8 (53.6)	394.0 (51.8)	409.3 (50.0)	393.1 (47.6)	352.3 (45.2)	330.9 (41.6)	302.0 (39.3)	296.3 (36.3)	329.7 (36.7)	4,425.0 (47.2)	-46.5[c]
Other non-retail	138.6 (12.6)	127.2 (13.2)	104.2 (12.3)	91.8 (12.1)	39.5 (12.8)	113.6 (13.8)	121.8 (15.6)	126.3 (15.9)	104.1 (13.6)	105.9 (13.0)	106.6 (11.9)	1,245.1 (13.3)	-23.1
Mail order	34.6 (3.1)	32.5 (3.4)	32.8 (3.9)	33.4 (4.4)	40.3 (4.9)	47.5 (5.8)	38.1 (4.9)	4,04 (5.1)	31.2 (4.1)	31.1 (3.8)	36.5 (4.1)	398.3 (4.3)	5.6
Retail	275.5 (25.0)	218.9 (22.7)	216.2 (25.6)	206.0 (27.1)	226.4 (27.7)	233.2 (28.3)	231.6 (29.7)	254.8 (32.0)	263.6 (34.3)	283.0 (34.7)	313.6 (35.1)	2,723.6 (29.1)	13.8[*]
Clinics	35.7 (3.2)	36.3 (3.8)	39.0 (4.6)	36.1 (4.7)	37.6 (4.6)	37.9 (4.6)	36.4 (4.7)	43.4 (5.5)	66.9 (8.7)	99.1 (12.2)	107.7 (12.1)	576.1 (6.2)	202.0[c]
Overall	1,100.4	963.4	844.9	761.3	818.6	825.3	780.0	795.8	767.8	815.4	894.1	9,367.1	-18.8

[a]All expenditures adjusted for inflation and reported in 2015 dollars

[b]Percent = specific care setting antifungal expenditures/total antifungal expenditures in that year

[c]$p<0.05$ estimated from simple linear regression analysis of trend over time in expenditures by healthcare setting

385 Table 2. Trends in antifungal expenditures and annual growth by class in the **clinic setting**

	Expenditures in $ millions (% annual growth)[a]											
Antifungal class	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total, 2005-2015
Polyenes	5.8	5.2 (-11.4)	4.6 (-9.92)	4.1 (-11.5)	3.7 (-8.9)	4.2 (12.5)	4.4 (4.3)	6.5 (47.1)	11.1 (72.4)	15.7 (40.7)	15.2 (-2.8)	805.1 (162.0)[b]
Triazoles	23.2	23.4 (1.2)	27.0 (15.2)	26.2 (-3.2)	28.3 (8.4)	28.5 (0.7)	27.1 (-4.7)	29.6 (8.9)	36.6 (23.5)	55.3 (51.2)	64.3 (16.2)	369.6 (177.8)[b]
Echinocandins	6.6	7.6 (14.4)	7.3 (-3.7)	5.6 (-22.5)	5.0 (-12.1)	4.5 (-9.3)	4.2 (-6.3)	6.2 (47.3)	17.1 (174.5)	24.2 (42.0)	20.1 (-16.8)	108.4 (204.9)[b]
Flucytosine	0.12	0.15 (25.4)	0.96 (-36.2)	0.18 (85.7)	0.57 (219.1)	0.68 (20.1)	0.55 (-19.1)	1.1 (99.6)	2.1 (93.5)	3.9 (82.9)	8.1 (106.8)	17.6 (6,640.9)[b]
All antifungals	35.6	36.3 (1.7)	39.0 (7.5)	36.1 (-7.5)	37.6 (4.3)	37.9 (0.9)	36.4 (-4.2)	43.4 (19.4)	66.9 (54.2)	99,1 (48.1)	107.7 (8.7)	576.1 (202.0)[b]

386 [a]All expenditures adjusted for inflation and reported in 2015 dollars

387 [b]$p<0.05$ estimated from simple linear regression analysis of trend over time in annual growth by

388 class

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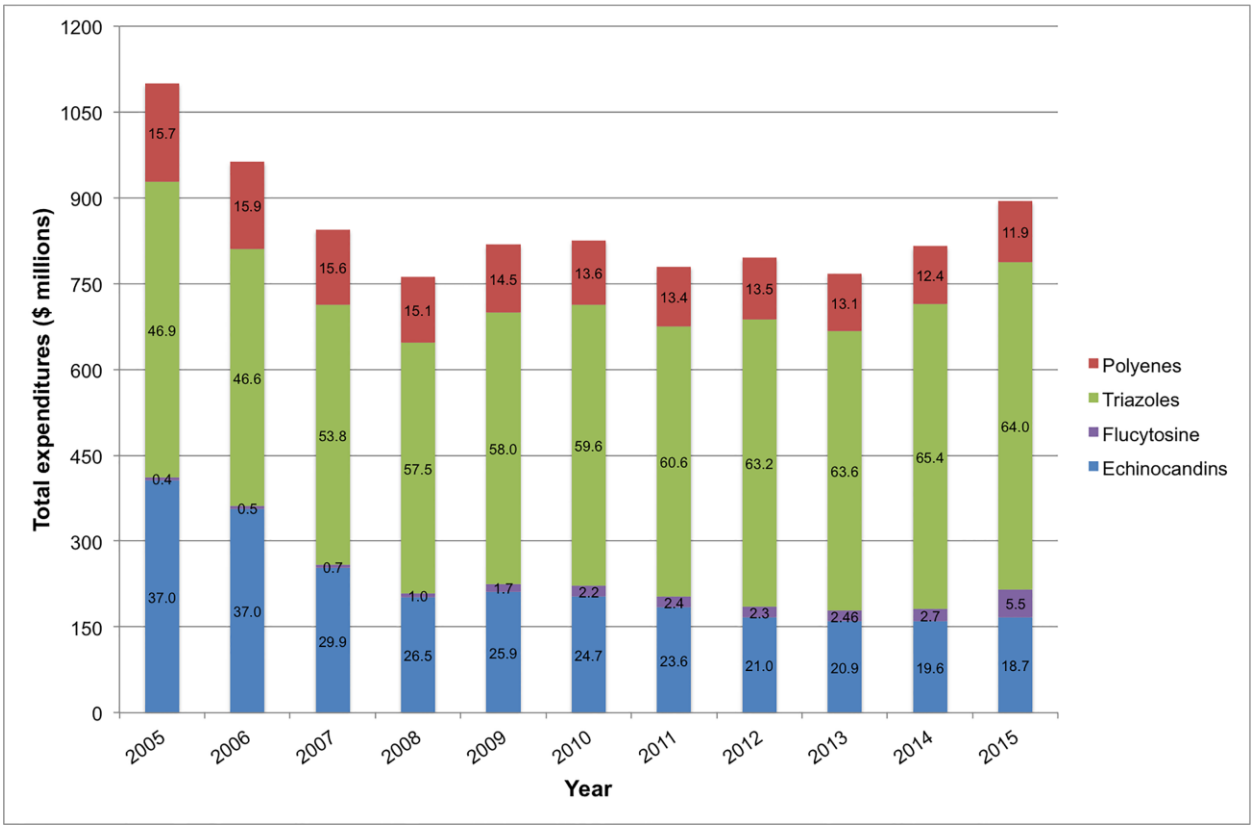
Total expenditures ($ millions)
1200
1050
900
750
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450
300
150
0
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Year
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0.4
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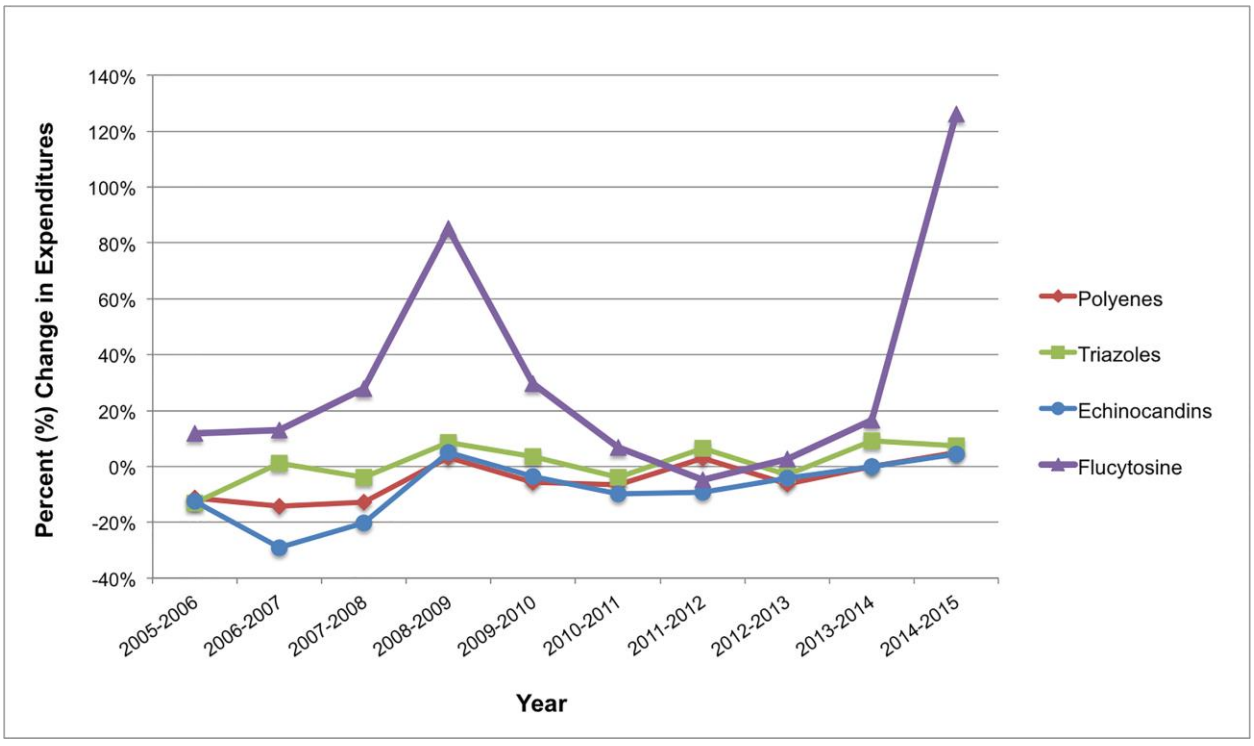
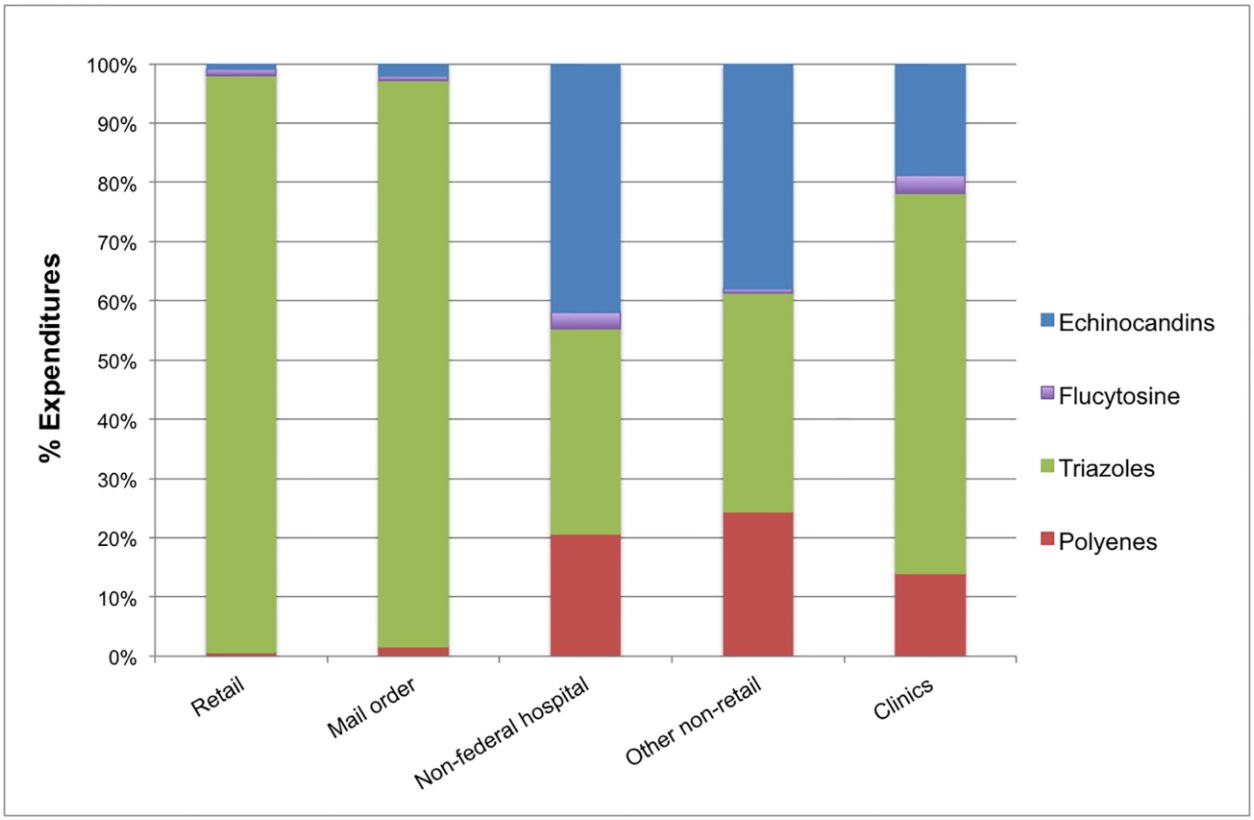
18.7
Polyenes
Triazoles
Flucytosine
Echinocandins

391

392


Percent (%) Change in Expenditures
140%
120%
100%
80%
60%
40%
20%
0%
-20%
-40%
2005-2006
2006-2007
2007-2008
2008-2009
2009-2010
2010-2011
2011-2012
2012-2013
2013-2014
2014-2015
Year
Polyenes
Triazoles
Echinocandins
Flucytosine

393


% Expenditures
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Retail
Mail order
Non-federal hospital
Other non-retail
Clinics
Echinocandins
Flucytosine
Triazoles
Polyenes