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Antifungal drug price increases in the United States, 2000–2019

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Abstract

Background: Antifungal drugs treat a variety of conditions, ranging from localised dermatologic disease to life-threatening systemic infections. Some common antifungal drugs experienced large price increases in recent years, however, factors contributing to these price increases are poorly understood. We sought to examine trends in antifungal drug prices and determine underlying drivers of price changes.

Methods: Antifungal drug products in the United States were identified using the Food and Drug Administration (FDA) Label database. For each product, we determined the wholesale acquisition cost per unit over time between 2000 and 2019, adjusting for inflation, and examined variables that could impact price: route of administration, number of FDA indications, the quantity of professional guideline recommendations, use for prophylaxis, number of FDA-approved manufacturers, and whether it was compounded. Price trajectories were clustered into four groups: (1) stable, 2) moderate, (3) high, and (4) extreme price increases.

Results: Of 139 identified drug products, one outlier was removed due to exorbitant price increases. Cluster 1 (n = 31) demonstrated the most stable prices with a 25% mean price increase. Clusters 2 (n = 97), 3 (n = 7), and 4 (n = 3) demonstrated moderate, high, and extreme price increases with 52%, 318%, and 900% mean price increases, respectively. Atypical routes of administration and compounding were over-represented in clusters 3 and 4. There was no correlation between the number of manufacturers and price changes.

Conclusions: Antifungal drugs exhibited large, inflation-adjusted price increases. Atypical routes of administration and compounding were over-represented within clusters exhibiting extraordinary price increases. Our data support policies aiming to curb large price increases for medically important drugs.

KEYWORDS
antifungal, cost, drugs, price

1 | BACKGROUND

Antifungal drugs are used for a wide variety of diseases, ranging from treating localised dermatologic infections to preventing and treating life-threatening systemic fungal diseases. Within the last decade, certain generic antifungal drugs, including fluconazole 50–200 mg oral tablets and nystatin 100,000 units/1 gram topical applications, have experienced steep price increases in the United States.[1] Yet, it is unknown if such price increases are common, what the underlying drivers are, or the clinical consequences of high costs for the healthcare system or individual patients. For patients with certain fungal infections requiring prolonged treatment durations—such as pulmonary aspergillosis and blastomycosis[2,3]—early drug discontinuation due to high out-of-pocket costs could lead to poor outcomes.

United States spending on prescription drugs has grown in recent decades, reaching $120 billion in 2018 and garnering increased attention from policymakers.[4] Available data suggest that limited manufacturer competition commonly drives large price hikes in the United States,[5–7] yet few studies have examined price trends specifically among antifungal drugs. One study found an inverse association between the number of manufacturers and changes in drug prices among topical dermatologic generic drugs, a subset of which were antifungal drugs.[8] Another study utilising Medicaid data between 1991 and 2009 suggests pricing may be more nuanced, with additional factors influencing the price of outpatient antifungal drugs, such as the introduction of new agents with expanded antifungal activity.[9]

There remains an incomplete understanding of the prevalence and magnitude of antifungal drug price increases in the United States. Additionally, identifying whether there are specific drivers for price increases, such as the number of manufacturers, indications, or professional recommendations, could provide helpful information for ongoing policy conversations. In this study, we sought to describe recent trends in antifungal drug price increases in the United States and identify factors associated with these price increases.

2 | METHODS

The primary objective of this study was to identify trends in antifungal drug prices in the United States between 2000 and 2019. We evaluated changes in the wholesale acquisition cost (WAC), which is a price benchmark set by drug manufacturers and represents the published list price of a drug. Although WAC does not reflect the actual cost paid for a drug, it represents the basis for drug payment negotiations throughout the drug supply chain and thus is pertinent to all US healthcare settings. For example, the price paid for a drug purchased at a retail pharmacy and a hospital is both impacted by the manufacturer-set WAC price. In this study, we did not analyse outpatient claims data or survey data on hospital drug spending, thus not allowing for comparisons between outpatient and inpatient spending on antifungal drugs.

The secondary objective was to determine if certain factors were associated with changes in WAC. Since the number of manufacturers has previously been found to be associated with drug price changes, [5–7] we included this factor. We also evaluated other characteristics that we thought could influence the price of a drug, including route of administration, whether a drug is compounded, number of US Food and Drug Administration (FDA) indications, number of professional guideline recommendations, and use for prophylaxis.

2.1 | Data extraction

First, we identified all FDA-approved antifungal drug products available in the United States through 2019 using the FDA Label Database (Table S1).[10] Next, we utilised the First Databank (San Francisco, CA) database to obtain the WAC for each National Drug Code (NDC), with the corresponding effective dates, from 01/2000 through 08/2019.[11] The WAC was determined by the unit of measure. The effective date represents the occurrence of a price change. Drug name, route of administration, formulation, and dose strength were also collected. Using the Medi-Span database (Hudson, OH), we collected the obsolete date and the Generic Product Indicator (GPI) for each NDC.[12] The obsolete date indicates when a drug is no longer being actively manufactured. The GPI is a unique number that encompasses multiple NDCs and reflects the active drug substance, strength, and formulation regardless of manufacturer. The GPI was used to define a drug product for the purposes of this study.

The remaining variables of interest were obtained from multiple sources. We obtained the number of approved manufacturer applications for each GPI using the Orange Book database, which is published annually by the FDA.[13] PDF copies of Orange Books from 2000 to 2018 were provided to us by request from the FDA via a Freedom of Information Act request. The online Orange Book database for 2019 was searched on 11/2019. If the Orange Book did not include a product correlating to a GPI, that GPI was presumed to represent a product from a compounding pharmacy. The number of FDA indications for each GPI was obtained using the Micromedex database (Greenwood Village, CO).[14] Finally, we reviewed the Infectious Diseases Society of America guidelines as of 11/2019 to quantify US professional society recommendations for a given antifungal product. These guidelines also identify if a drug was recommended for prophylactic use. At that time, guidelines were available for the treatment of aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, and sporotrichosis.[2,3,15–19] Additional details about the variable selection and data extraction are provided in Supplemental Material pages 1 and 16.

2.2 | Statistical analyses

We sought to identify drug pricing trends using an unsupervised clustering approach. Typical clustering methods using Euclidean distance would not be sufficient to identify similar shapes that

occur at different points in time. More appropriately, we applied a clustering methodology that clusters drugs based on the shape of their price trajectory (Supplemental Material pages 13–14). To create the trajectories, we first calculated the percent change in price from baseline at each effective date for an NDC. These percent changes across all effective dates for all NDCs within a GPI were then gathered and ordered across time. This allowed us to plot the price trajectory during the time a GPI is active. An illustrative example is provided in the Supplemental Material pages 8–11. The average price change for one drug product represents the mean percent price change across all effective dates for all NDCs associated with the GPI that defines that drug product. We then grouped the products that exhibit similar trajectories of price change, regardless of temporality (Figure S6).

Price data were adjusted for inflation using the R package priceR [15.5][20] with cost reported in US dollars, the year 2019 values. The inflation-adjusted price trajectories of the antifungal drug products were clustered into four groups by the shape of their trajectory using the R package KmlShape.[21] We did not conduct a sensitivity analysis for costs with different annual discount rates due to the descriptive nature of the study objectives and the decision to use WAC for analyses, which is a standard measure of the drug product cost.

To determine if drug product characteristics were associated with cluster membership, statistical analyses were conducted at the 5% level of significance using the R statistical programming language.[22] Fisher's Exact Tests[23] were used to test the association between cluster membership and categorical drug product characteristics, including route of administration, number of professional guideline recommendations, use for prophylaxis, and if it is from a compounding pharmacy. A drug product's route of administration was categorised as intravenous (including injection), oral, topical, vaginal, or atypical route (including buccal and mucous membrane). The number of professional guideline recommendations was categorised as <5, 5–39, and ≥40. A drug product's recommendation for prophylaxis and compounding status were binary variables.

The number of FDA indications is an over-dispersed count variable; thus, a negative binomial generalised linear model[24] was fit to the subset of data that had an indication value. The likelihood-ratio chi-squared test was used to determine if cluster membership is a significant explanatory variable for the number of FDA indications. Finally, to analyse the relationship between the number of manufacturers and a drug product's price over time, we calculated the correlation between these two lists. This process excludes compounded drug products and those with no change in manufacturers. This process is detailed and illustrated in Supplemental Material pages 22–24.

3 | RESULTS

A total of 139 antifungal drug products, representing 27 different active substances, met inclusion criteria (Table S1). The presence of one outlier with a massive price increase (compounded nystatin 500 mm unit powder, which increased by >9000%, from $2.74 in 2001 to $264.09 in 2011; Figure S5 and Table S3) prevented effective clustering and was removed from subsequent analyses. Among the remaining 138 antifungal drug products, there were 2615 occurrences of a price change with an average price increase of 127%. The price trajectories were clustered into four groups, which were characterised by their degree of price changes over time. Antifungal drug products in Cluster 1 (n = 31) were most stably priced with an average price increase of 25%. Cluster 2 (n = 97) comprised the majority of drug products, with an average price increase of 52%. Cluster 3 (n = 7) comprised drug products with an average price increase of 318%, and cluster 4 (n = 3) comprised drug products demonstrating extreme price increases, with an average price increase of 900% (Table 1). The names and characteristics of the antifungal drug products represented in Clusters 3 and 4 are listed in Table 2.

Topically applied drug products were the most common (n = 52), followed by oral (n = 32), vaginal (n = 23), intravenous (n = 20), and atypical routes (n = 11). The majority of drug products had <5 professional guideline recommendations (n = 100), followed by >40 (n = 23) and 5–39 (n = 15) (Figure S10). Of the drug products with FDA indications for use (n = 128), the majority had five or fewer indications (n = 102) and the most indications for a product were 18. Seventy-one drug products entered the study with one manufacturer, 14 with two, and 21 with at least three manufacturers. During the study period, 31 drug products increased from one to at least three manufacturers. There were 32 compounded drug products.

Drug products with atypical routes of administration (routes that did not include oral, intravenous, topical, or vaginal) were overrepresented within Clusters 3 and 4 (p = .005). Similarly, drug products that were produced by one or more compounding pharmacies were also overrepresented within Clusters 3 and 4 (p = .03). The average number of FDA indications, number of professional guideline recommendations, and prophylaxis recommendations for each drug product were not significantly different across cluster membership (p = .33, .65, and .99, respectively) (Table 1). Finally, after excluding compounded drug products and drugs with no change in the number of manufacturers over time, the average correlation between the number of manufacturers and price over time (overall and within clusters) was near zero, indicating no association (Table 1, Figure S12). Among drug products that entered the study period with a single manufacturer and increased to 3 or more manufacturers (n = 31), the average correlation was negligible, indicating there was no difference in price with additional manufacturers (p = −.23) (Figure S13).

4 | DISCUSSION

Between 2000 and 2019, large inflation-adjusted price increases of antifungal drug products were common. Using a cluster model, we found that approximately two-thirds (n = 97) of antifungal drug

TABLE 1 Antifungal price changes by cluster membership and drug characteristics, 2000–2019

	Cluster 1 ($n = 31$)	Cluster 2 ($n = 97$)	Cluster 3 ($n = 7$)	Cluster 4 ($n = 3$)	p Value
Number of price change occurrences	179	2049	221	166	n/a[a]
Average percent price change (range)	25.2% (−28.8, 109.8)	52.4% (−97.3, 936.8)	318.1% (−92.1, 3530.5)	899.6% (−90.6, 6023.9)	n/a[a]
Route of administration (%)	IV = 4 (13%) ATYP = 4 (13%) PO = 7 (23%) TOP = 12 (39%) VAG = 4 (13%)	IV = 16 (17%) ATYP = 3 (3%) PO = 21 (22%) TOP = 38 (39%) VAG = 19 (20%)	IV = 0 (0%) ATYP = 3 (43%) PO = 4 (57%) TOP = 0 (0%) VAG = 0 (0%)	IV = 0 (0%) ATYP = 1 (33%) PO = 0 (0%) TOP = 2 (67%) VAG = 0 (0%)	**.005**
Average number FDA indications[b] (min/max)	3.2 (1, 11)	3.7 (1, 18)	3.9 (2, 9)	1 (1, 1)	.33
Average number professional guidelines	7.2	11.3	11.6	0.3	.65
Recommendation for prophylactic use (%)	5 (16%)	17 (18%)	1 (14%)	0 (0%)	.99
Compounded drug product (%)	12 (39%)	16 (16%)	3 (43%)	1 (33%)	**.03**
Average number of manufacturers[c] (min, max)	1.2 (1, 3)	3.0 (0, 15)	5.4 (1, 14)	4.2 (2, 11)	n/a[d]

[a] Association not assessed; data provided as a description of statistical clustering results only.

[b] Included 128 drug products with FDA indication data available (Cluster 1, $n = 25$; Cluster 2, $n = 94$; Cluster 3, $n = 7$; and Cluster 4, $n = 2$).

[c] Included 68 drug products with aligned data for manufacturers and price changes (Cluster 1, $n = 4$; Cluster 2, $n = 58$; Cluster 3, $n = 4$; and Cluster 4, $n = 2$).

[d] This variable was assessed using correlation (near zero).

Bold values indicate $p > 0.05$.

TABLE 2 Antifungal drug products in clusters 3 and 4

Name	Strength	Formulation	Route	Average % price change per unit (range)	Average $ price change per unit (range)
Cluster 3					
Clotrimazole (Topical)	(Compounded)	Powder	Atypical	377% (4%, 2407%)	$2.31 ($0.10, $7.98)
Fluconazole	150 mg	Tablet	Oral	83% (−92%, 1797%)	$7.91 (−$4.34, $46.12)
Flucytosine	250 mg	Capsule	Oral	558% (3%, 1680%)	$27.72 ($0.13, $78.32)
Flucytosine	500 mg	Capsule	Oral	542% (3%, 1631%)	$53.45 ($0.28, $151.30)
Miconazole	(COMPOUNDED)	Powder	Atypical	404% (−20%, 2346%)	$7.82 (−$7.47, $35.13)
Miconazole nitrate (Topical)	(compounded)	Powder	Atypical	364% (−6%, 1530%)	$4.81 (−$0.98, $16.53)
Nystatin (mouth–throat)	100,000/ml	Oral suspension	Oral	191% (−61%, 3531%)	$0.05 (−$0.18, $0.29)
Cluster 4					
Amphotericin B (Mouth-Throat)	(Compounded)	Powder	Atypical	417% (−54%, 4256%)	$23.00 (−$14.99, $452.52)
Nystatin-Triamcinolone	100,000/1 mg	Ointment	Topical	1288% (−91%, 6026%)	$1.35 (−$3.33, $6.43)
Nystatin-Triamcinolone	100,000/1 mg	Cream	Topical	1308% (−78%, 6026%)	$1.48 (−$4.99, $6.41)

products increased in price by around 50%, on average, and 20% ($n = 31$) of products increased by 25%. Clusters exhibiting extraordinary price increases of 300% or more comprised the minority of drug products (7%, $n = 10$) and were associated with compounding and atypical routes of administration. Notably, we did not identify any clusters with a decrease in average price despite including data that spanned two decades. Similarly, there was no correlation between the number of drug manufacturers and price changes.

Our findings are concerning because drug discontinuation from high out-of-pocket spending is a risk and may have serious and life-threatening clinical consequences for patients. Although we did not examine out-of-pocket spending, recent data has shown that WAC increases affecting brand-name drugs are associated with increases in out-of-pocket spending among patients paying deductibles and co-insurance.[25] Prior work has documented that when out-of-pocket costs increase, especially above $125,

patients are more likely to abandon prescriptions at pharmacies.[26] If prices increase for drugs that are first-line, there may be a transition to alternative, second-line options which may lead to worse outcomes. Switching from the first-line anti-parasitic drugs, albendazole, and mebendazole to second-line drugs due to cost was recently described.[27] This was also a pressing concern with flucytosine, a first-line drug used in the treatment of cryptococcosis. Flucytosine experienced a drastic increase in price,[28] which was alleviated somewhat with a subsequent price reduction attributed to market competition and significant advocacy work to increase competition and distribution.[29,30]

That compounded drug products and atypical routes of administration were overrepresented in clusters exhibiting extraordinary price hikes suggest that antifungal drug products which are niche, or treat a relatively small population, may be more vulnerable to large price increases. Indeed, large price hikes of anti-infective medications that treat small populations—and for which there are often limited therapeutic options—is a common occurrence.[31,32] We found that amphotericin B, used as a compounded suspension, increased from $2.72 per unit WAC in 2001, to $118.69 per unit WAC in 2012, an increase of 4000%. This drug was historically considered a therapeutic option for treating fluconazole-refractory oral candidiasis,[33] an infrequently encountered condition.

A notable finding was that we found no correlation between the number of manufacturers and price changes—even among the 20% of anti-fungal products that increased from having one to at least three manufacturers during our study period. This finding is in contrast to prior studies that show limited market competition is associated with large price increases among generic prescription drugs.[7,34] There is some evidence that the association between market competition and the number of manufacturers may be decreasing with time,[35] and our study may be capturing this phenomenon. Alternative explanations for our findings are that the antifungal drug market may be less sensitive to market competition, or that we may have been underpowered to detect an association between price changes and the number of manufacturers.

4.1 | Limitations

Our study has several limitations. First, we did not account for the timing of drug price changes (i.e., differentiating a price change that occurred 15 vs. 5 years ago) which limits the ability to describe trends in relation to the timing of legislative and other interventions attempting to curb rising drug prices since 2000. Second, our assessment of the impact of professional society guidelines on price changes is limited as most of the infectious disease guidelines relate to the use of systemic antifungal therapy, not topical antifungals. Additionally, the ability to capture the impact of manufacturer competition on drug pricing using FDA Orange Book data is limited, as manufacturers may choose not to sell a drug product for which they are approved and products may also continue to be sold after a drug is discontinued by the manufacturer. Third, because we did not use claims data to assess which NDCs within a given GPI were used most frequently, our ability to assess the real-world impact of a given price change was limited. Fourth, although WAC price increases do result in higher healthcare system costs that are often passed on to patients, WAC is an imperfect measure that does not reflect the true cost of a drug. The price paid by the end-user is influenced by a number of factors, such as pharmacy-distributor purchasing agreements, rebates negotiated between pharmacy benefit managers and manufacturers, and healthcare insurance coverage. Finally, because we did not use claims data, we did not examine other important factors that influence the total and out-of-pocket cost of a drug, including a patient's insurance status and insurance plan design, the setting in which a patient has prescribed a drug (i.e., inpatient vs outpatient setting), and the use of copayment offsets.

More research is needed to understand the impact that price increases have on out-of-pocket spending and clinical outcomes. Specifically, the lack of an association between manufacturer competition and price changes for antifungal drug products in our study warrants further research to better understand the role of market competition in antifungal drug pricing. As US healthcare spending on prescription drugs continues to outpace inflation,[36,37] policymakers have become increasingly engaged in developing legislation to prevent large drug price increases. Our data provide additional rationale for policies aiming to curb large drug price increases occurring beyond inflation.[38,39]

AUTHOR CONTRIBUTIONS

Christine Thomas: investigation, writing—original draft preparation, writing—review and editing; **Whitney Shae:** formal analysis, writing—review and editing; **Devin Koestler:** formal analysis, writing—review and editing; **Terese DeFor:** data curation; **Nathan Bahr:** conceptualisation, investigation, writing—review and editing; **Jonathan Alpern:** conceptualisation, investigation, writing—review and editing, supervision.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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