Influence of Market Competition on Tetracycline Pricing and Impact of Price Increases on Clinician Prescribing Behavior

John S. Barbieri¹, David J. Margolis¹,² and Bruce A. Brod¹

Oral tetracyclines are commonly used for acne and other conditions. Recent generic price increases threaten access to these medications. Using the OptumInsight Clininformatics DataMart, we retrospectively evaluated the underlying factors behind these price increases for oral tetracyclines using the framework of a competitive market and evaluated the impact of these price increases on prescribing practices. Between 2011 and 2013, the mean cost of doxycycline hyclate prescriptions increased from $7.16 to $139.89 and the mean out-of-pocket cost increased by $9.69. A comparable cost increase was not observed for doxycycline monohydrate or minocycline. There was no significant association between the cost of doxycycline hyclate and market concentration as assessed by the Herfindahl-Hirschman index ($\beta = 0.030$, 95% confidence interval $-0.019$ to $0.079$, $P = 0.213$) and the market was highly concentrated throughout the study period. The percentage of prescriptions for doxycycline hyclate decreased by 1.9% from 2011 to 2013. This dramatic increase in the cost of doxycycline hyclate is not easily explained using the framework of a competitive market, suggesting that noncompetitive market forces may be responsible. In addition, clinicians have not altered their prescribing behavior in response to this price increase, suggesting that clinician or pharmacy level interventions could potentially increase the use of less costly substitutes.


INTRODUCTION

In 2015, U.S. health care spending on retail prescription drugs increased by 9% to $324.6 billion, accounting for 10% of overall health care expenditures (Centers for Medicare and Medicaid Services et al., 2016). Although costs for generic medications have been declining overall, a subset of established generic medications have had significant price increases in recent years (U.S. Government Accountability Office, 2016). This problem is especially prevalent in dermatology (Albrecht et al., 2016). Although topical medications represent only 8% of all established generic medications evaluated in a recent report by the Government Accountability Office, 46% of generic medications with price increases of more than 100% between 2011 and 2012 were topical medications (U.S. Government Accountability Office, 2016).

In addition, a 2016 survey of retail prices for 19 commonly prescribed brand-name topical and systemic medications in dermatology at four national chain pharmacies found that the mean increase in price was 401% during the 6-year survey period (Rosenberg and Rosenberg, 2016). A recent study examining copays and costs of commonly prescribed topical corticosteroids found significant variation in pricing across similar agents (Skojec et al., 2015); it has been estimated that if prescribers were to consistently prescribe the least expensive generic topical corticosteroid within their potency group, Medicare potentially could have saved more than $422 million in 2015 and out-of-pocket costs for Medicare beneficiaries would have been reduced by more than $25 million in 2015 (Song et al., 2017). Given that cost is a significant factor influencing patient adherence, these rising costs threaten patients’ ability to access needed treatments and fluctuating prices among common generic medications challenge clinicians’ ability to prescribe patients the most cost-effective therapies (Doshi et al., 2016a, 2016b).

We sought to understand the underlying factors behind these price increases and their impact on provider prescribing behavior. Because the market for generic medications should behave like a competitive market, we chose to use this framework for our analysis with a focus on factors influencing manufacturers (supply), factors influencing the use of the medication by patients and clinicians (demand), and the overall structure of the market. In this framework, increases in the costs to produce the medication, increases in demand from patients and clinicians for the medication, and increases in market share that give manufacturers a monopoly or near-monopoly are all potential mechanisms that could result in an increase in the price of the medication.

Specifically, using the deidentified OptumInsight Clininformatics DataMart (OptumInsight, Eden Prairie, MN), we examined the market for oral tetracycline-class antibiotics commonly used for acne (i.e., doxycycline, minocycline) with a focus on the dramatic increase in the price of...
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doxyccycline hyclate in 2012–2013 (U.S. Government Accountability Office, 2016). We examined the cost of prescriptions for doxycycline hyclate, doxycycline monohydrate, and minocycline from 2004 to 2014, including an evaluation of patient out-of-pocket costs. In addition, we calculated the Herfindahl-Hirschman index (HHI), which is a commonly accepted measure of market concentration used by the Department of Justice, to evaluate the impact of changes in the market share of the manufacturers of these antibiotics on price (Department of Justice, 2015).

RESULTS

Antibiotic pricing
Between 2011 and 2013, the mean cost of a prescription for doxycycline hyclate increased by 1,854% from $7.16 to $139.89. In contrast, the mean cost of a prescription for doxycycline monohydrate increased by 8% and the mean cost for a prescription for minocycline increased by 2% during this time period. Between 2011 and 2013, the mean total out-of-pocket cost, which comprises copay cost and deductible cost, of a prescription for doxycycline hyclate increased by $9.69, representing a 102% increase, with the percentage of patients with total out-of-pocket costs of $50 or more per prescription increasing 50-fold from 0.1% to 6.8%. In contrast, the mean out-of-pocket cost of a prescription for doxycycline monohydrate increased by 26% and the mean out-of-pocket cost of a prescription for minocycline increased by 1% during this time period (Figure 1). Similar relative changes in price were observed for both prescriptions written for a 1-month supply and those written for a 3-month supply in our subgroup analyses (Supplementary Figure S1 online).

Market structure
The markets for doxycycline hyclate, doxycycline monohydrate, and minocycline all have an HHI of greater than 2,500 throughout the study period (Figure 2), which would define these markets as highly concentrated based on criteria used by the Department of Justice (2015). We did not identify a significant association between the cost of doxycycline hyclate and the HHI over the study period (β = 0.030, 95% confidence interval −0.019 to 0.079, P = 0.213).

Prescribing behavior
In the setting of this price increase for doxycycline hyclate, the percentage of prescriptions for doxycycline hyclate given to patients being treated for acne decreased by 1.9% from 2011 to 2013. The percentage of prescriptions using doxycycline monohydrate increased by 2.5%, from 2011 to 2013. The percentage of prescriptions using extended-release doxycycline formulations increased by 0.1% from 2011 to 2013. The percentage of prescriptions using minocycline increased by 3.9% from 2011 to 2013. The percentage of prescriptions using extended-release minocycline formulations decreased by 4.6% from 2011 to 2013 (Figure 3).

Potential savings
If clinicians were to prescribe the least expensive oral tetracycline-class antibiotic in the place of doxycycline hyclate in 2013, this change would result in savings of $105.13 per prescription of antibiotics and would reduce patient out-of-pocket expenditures by $5.77 per prescription. Amongst the entire patient population with acne being treated with oral tetracycline-class antibiotics available in the OptumInsight Clinformatics DataMart, these potential savings would amount to $10.7 million and would reduce patient out-of-pocket expenditures by $761,000 in 2013.

DISCUSSION
Between 2011 and 2013, the mean cost of a prescription for doxycycline hyclate increased dramatically from $7.16 to $139.89, representing a 1,854% increase in price. In contrast, comparable price increases during this timeframe are not observed for other oral tetracycline-class antibiotics, such as doxycycline monohydrate and minocycline. This dramatic price increase was also associated with increased out-of-pocket expenditures for patients, increasing the financial burden of health care and potentially threatening access to care. In response to this price increase, we do not observe a significant shift in provider prescribing behavior to less costly therapeutic alternatives.

When evaluating the contributing factors associated with a change in price in the marketplace, it is helpful to consider costs of production, factors influencing the use of the medication by patients and clinicians, and market structure. With respect to costs of production, doxycycline hyclate, doxycycline monohydrate, and minocycline all likely share similar input costs, regulatory burden, and marketing and distribution costs. As a result, if an event causing an increase in manufacturing costs (e.g., new more stringent manufacturing requirements) were to be responsible for this dramatic price increase, we would expect to see similar associated price increases for doxycycline monohydrate and minocycline, which are not observed. In addition, although doxycycline hyclate had a lower price than doxycycline monohydrate or minocycline in 2011, in a competitive market, without an increase in the cost to produce the medication, manufacturers should not be able to successfully increase the price nearly 2,000% to match that of these other oral antibiotics without a potential competitor undercutting their price.

With respect to factors influencing the use of the medication by patients and clinicians, doxycycline hyclate, doxycycline monohydrate, and minocycline have similar therapeutic indications, so it is unlikely that the demand for doxycycline hyclate increased dramatically and disproportionately compared with doxycycline monohydrate and minocycline. In addition, we are not aware of any major new therapeutic indications for these medications around the time of this dramatic price increase. As a result, it is unlikely that increased demand for doxycycline hyclate can explain the observed increase in the price.

Finally, changes in market structure are important to consider. For instance, if a major manufacturer of doxycycline hyclate merged or went out of business, this process could increase market concentration and allow the suppliers of doxycycline hyclate to charge prices closer to that of a monopoly, thus increasing the cost of doxycycline hyclate. Recently published work has identified an association between market competition, as assessed by the HHI, and generic drug price increases (Dave et al., 2017). However, although the market for doxycycline hyclate is concentrated throughout the study period, we do not observe a notable increase in market concentration, as assessed by the HHI,
around the time of this price increase. In addition, we do not identify an association between market concentration and the price of doxycycline hyclate.

Given that it is difficult to explain the dramatic increase in the cost of doxycycline hyclate between 2011 and 2013 using the framework of a competitive market, noncompetitive market factors must be considered as the underlying cause of this price increase. Of note, there have been recent inquiries by the Department of Justice and others into companies involved in the manufacture of doxycycline hyclate, suggesting that potentially anticompetitive behavior may be responsible for this dramatic price increase (Bloomberg, 2016; McElhaney, 2017). Interestingly, throughout the study period, the generic market for these antibiotics is highly concentrated, as defined by an HHI of greater than 2,500. This highly concentrated marketplace may provide a scenario prone to anticompetitive behavior given the relative lack of market participants. Alternatively, these highly concentrated markets may be at a tipping point between functioning as a competitive marketplace and a monopoly. Although we do not observe an association between HHI and price, these markets may behave in a nonlinear fashion that we are unable to model effectively in our analysis. Nevertheless, these markets do not appear to be functioning effectively as competitive markets for generic medications.

If anticompetitive behavior is ultimately found to be responsible for these price increases, identifying potential strategies to build a more competitive marketplace by increasing the number of market participants would represent a potential strategy to reduce the likelihood of similar behavior occurring in the future. Potential interventions could include reducing barriers to entry or allowing for reimportation of medications in the setting of shortages or dramatic price increases. Another strategy would be to require generic drug manufacturers to justify dramatic price increases, and Maryland has recently established legislation authorizing the attorney general to prosecute generic manufacturers in the setting of unconscionable price increases (Greene and Padula, 2017). Finally, although there has been discussion of statutory price controls and concentrating market power among purchasers (e.g., Medicare), such an approach would need to be balanced with maintaining access to the full compendium of medications (McCarthy, 2015).

The lack of adjustment in prescribing behavior in response to this price increase is a concerning issue. In a functioning market with rational market participants, if one good experiences a dramatic price increase, consumers would be expected to shift some of their purchasing to substitutes, especially if these alternatives have relatively similar features to the good that has experienced the price increase. In the case of these antibiotics, doxycycline monohydrate and minocycline are reasonable therapeutic alternatives to doxycycline hyclate in the treatment of acne (Garner et al., 2012; Zaenglein et al., 2016). As a result, clinicians potentially could address this dramatic increase in the price of doxycycline hyclate by shifting their prescribing practices toward these less costly substitutes. However, in our data, we do not observe any considerable evidence of clinicians shifting their prescribing practices to less costly antibiotics. In fact, even the slight increase in the use of minocycline may be due to the corresponding decrease in the use of extended-release formulations of minocycline rather than a shift from doxycycline hyclate.

It is not surprising that we do not observe clinicians altering their prescribing behavior in response to this price increase given that price information is not transparent to patients or clinicians. In addition, by disassociating total costs to the

Figure 1. Mean cost of generic oral tetracycline-class antibiotics between 2004 and 2014. (a) The mean standard cost, (b) mean patient copay, and (c) mean patient deductible for doxycycline hyclate, doxycycline monohydrate, and minocycline.
evaluation of tetracycline price increases

Figure 2. Herfindahl-Hirschman index for generic oral tetracycline-class antibiotics between 2004 and 2014. The Herfindahl-Hirschman index was calculated by extracting the labeler section of the National Drug Codes available for each prescription in the dataset to identify the market share of each manufacturer of doxycycline hyclate, doxycycline monohydrate, and minocycline during the study period.

Figure 3. Relative use of oral tetracycline-class antibiotics between 2004 and 2014 in the treatment of acne. ER, extended release.

There are a variety of potential approaches to address these issues including providing clinicians with real-time pricing information at the point of care, therapeutic interchange policies, automatic substitution at the pharmacy level, and training to reduce cognitive bias; future work is needed to best identify how to improve the ability of clinicians to respond to price increases in the marketplace (Kirby and Miller, 2017). Given that the potential savings to the health system in 2013 by prescribing the least costly oral tetracycline-class antibiotic in the place of doxycycline hyclate were more than $10 million among the patients in our dataset, which represent only a fraction of the entire U.S. population, it is likely that the potential impact of these types of interventions could be substantial. In addition, as health care reform places a greater emphasis on the cost of care, identifying cost-effective prescribing practices will become increasingly important for clinicians (Barbieri et al., 2017).

Strengths and limitations

This paper has several strengths including its large, nationally representative sample of patients included in the OptumInsight Clinformatics DataMart. In addition, the use of standard cost reduces the impact of inaccuracies associated with using other measures of cost such as average wholesale price or charge (Gencarelli, 2002). The results of our study should be interpreted in the context of the study design. Although standard cost is likely more accurate than either average wholesale price or charge in assessing the cost of filling prescriptions, it is still possible that complex payment structures, rebates, and coupons could result in different costs to the health system and to patients from our estimates. However, given that we are most interested in evaluating relative changes in cost for these oral antibiotics, our results should still represent a helpful estimate of the direction and relative magnitude of changes in price during our study period. Furthermore, although rebates and coupons have become commonplace for branded medications, they are not used in the generic medication market where multiple suppliers producing the same product make them difficult to implement. In addition, because the cost of a 3-month supply is typically greater than that of a 1-month supply, if prescribers were to shift toward prescribing a 3-month supply instead of a 1-month supply, that would result in the appearance of a price increase in our results that was instead a reflection of changing prescribing practices. However, the majority of prescriptions in our analysis dataset are for a 1-month supply and we observe similar findings in our subgroup analysis of prescriptions written for a 1-month supply and for a 3-month supply, which suggests that a change in prescription duration is not responsible for the price increases observed in our study. Finally, although the OptumInsight Clinformatics DataMart is a broadly representative claims database, it does not include complete information on the entire U.S. market, and if patients in our dataset were more likely to receive medication from specific manufacturers, our estimates of market share could become biased from the true distribution. In addition, if the insurers covering these patients were to
negotiate different special pricing agreements for these oral antibiotics, our estimates of price could differ from the actual price across all insurers. Although such selective negotiating has occurred for some extremely costly specialty medications (Humer, 2014), we are not aware of such a practice for the oral antibiotics evaluated in this study. Finally, the observational design of this study prevents us from being able to identify causal relationships.

Conclusions
Our study highlights that some generic medications have experienced extraordinary price increases in recent years and that in the case of doxycycline hyclate, nonmarket forces may be responsible for this price increase. In addition, we find that clinicians have not significantly altered their prescribing behavior in response to this price increase, suggesting that clinician level or pharmacy level interventions could potentially help increase the use of less costly therapeutic substitutes when they are available.

MATERIALS AND METHODS
Data source
This study was a retrospective analysis of the OptumInsight Clinformatics DataMart between 2004 and 2014, which contains de-identified commercial claims data for approximately 12–14 million annual covered lives in the United States. These data include both medical and pharmacy claims. The pharmacy claims report information on the medication dose, strength, and count, as well as the average wholesale price and charge for the prescription and the copay and deductible costs to the patient. In addition, to alleviate the weaknesses associated with using average wholesale price to assess the cost of pharmacy claims, the OptumInsight Clinformatics DataMart includes an additional variable, standard cost, that is a proprietary estimate attempting to more accurately reflect the total cost of the claim (Gencarelli, 2002). Prices are indexed to the year 2014.

Study design and study population
Prescriptions as ordered regardless of the length or quantity of the order for doxycycline hyclate, doxycycline monohydrate, minocycline, doxycycline extended-release preparations, and minocycline extended-release preparations that were prescribed to patients with at least one claim associated with an International Classification of Diseases Ninth or Tenth Revision code for acne identified by their associated National Drug Codes were our primary unit of analysis. We limited our analysis to prescriptions of at least 30 days in duration to reduce the likelihood of capturing prescriptions for acute illnesses. In addition, we conducted subgroup analyses of prescriptions written for a 1-month supply and for a 3-month supply to evaluate whether there are differences between prescriptions written for these durations.

Identification of manufacturer market share
National Drug Codes are 10- or 11-digit unique identifiers managed by the Food and Drug Administration and assigned to all drugs manufactured, prepared, propagated, compounded, or processed by a business entity for commercial distribution (Food and Drug Administration). These identifiers contain three sections: the first section identifies the labeler or manufacturer of the medication, the second section identifies the product, and the third section identifies the package size. We extracted the labeler details from each pharmacy claim and used it to identify the manufacturer of the medication that was filled by the patient. Subsequently, we summed this manufacturer information for all prescriptions of a given medication to develop an understanding of the market share of each manufacturer in the market (i.e., the market structure). Finally, we used this information to calculate an index of market concentration and changes in this index over time.

We used the HHI as our measure of concentration. The HHI is a commonly accepted measure of market concentration and is used by the Department of Justice to assess potential mergers. The HHI is defined as the sum of the squares of the market share of each manufacturer in the market. The HHI ranges from 0 to 10,000, with larger numbers representing higher levels of concentration. The index approaches 0 when there are large numbers of firms each with small market shares (e.g., if there are 1,000 firms each with a 0.1% share, the index equals 10; if there is one firm with a 100% share, the index equals 10,000). The Department of Justice defines an HHI of <1,500 as a competitive market, 1,500–2,500 as a moderately concentrated market, and >2,500 as a highly concentrated market (Department of Justice, 2015).

Statistical analysis
Descriptive statistics are presented using means, medians, and percentages as appropriate for our outcomes of interest. In addition, least-squares regression was used to assess for an association between cost and the HHI:

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\text{Standard cost} = \beta_0 + \beta_1 \times \text{HHI},
\]

where \(\beta_0\) represents the intercept and \(\beta_1\) the slope coefficient. Statistical analyses were performed in Stata 14 (StataCorp, College Station, TX). The Institutional Review Board of the University of Pennsylvania has granted a blanket exemption for all research completed at the University of Pennsylvania using OptumInsight data. This manuscript was prepared in accordance with the STROBE statement (von Elm et al., 2007).

ORCID
John S. Barbieri: http://orcid.org/0000-0002-5467-4102

CONFLICT OF INTEREST
The authors state no conflict of interest.

SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2017.07.835.

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