

Differences in drug prices by formulation

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Key points

QUESTION

For medications available in multiple formulations, are there significant price differences between formulations, and what are the opportunity for savings if prescribers ordering the more expensive formulation switched to the less expensive formulation?

FINDINGS

Price differences across formulations exceeded 4,000% for certain medications. Prescribing of lower cost formulations could result in a 24% reduction in spending on medications available in multiple formulations.

MEANING

Solutions to encourage and facilitate prescribing of lower-cost formulations can offer a means to reduce drug spending with potentially minimal impacts on quality.

Abstract

IMPORTANCE

Reducing drug spending growth is a policy priority. Solutions to encourage and facilitate prescribing of available appropriate, lower-cost medication alternatives have been pursued. One dimension on which price may vary is formulation. Switching to lower-cost formulations could offer a means to reduce drug spending while maintaining clinical equivalency.

OBJECTIVE

To estimate whether there are significant price differences between drug formulations, to quantify the proportion of medication orders for which a lower-cost formulation was available for the same medication, and to simulate the opportunity for savings if lower-cost formulations are prescribed when available.

DESIGN

We focus on medications available in multiple formulations: tablet and capsule (for non-extended release and extended release medications) or ointment and cream. A large database on medication orders was obtained from Gemini Health, which provides real-time benefits check solutions to health care systems. The data contained detailed order-level information including the formulation-specific medication, the insurer- and pharmacy-specific negotiated price, quantity, pharmacy, and the patient's insurer.

SETTING

Medication orders for a large commercially-insured population located in California, Minnesota, and New Jersey in August 2019.

OUTCOMES

Percentage difference in the negotiated price between formulations. Percentage of orders initiated for the more expensive formulation. The savings that would have resulted if the less expensive formulation had been prescribed instead.

RESULTS

The price difference between formulations differed across medications. Among all the medications examined, venlafaxine-75mg had the greatest price difference across formulations estimated at 4,208% ($p < 0.001$). Across medications, the same formulation was not consistently more expensive. Forty percent of orders in our sample were initiated for the more expensive formulation. If these orders had instead been placed for the lower-cost formulation, spending on the medications studied would have been 24% lower.

CONCLUSIONS AND RELEVANCE

Medication prices differ vastly by formulation, and such price differences offer opportunity to lower drug spending through prescribing of lower-cost formulations when available. However, because the lowest cost formulation differs by medication, tools such as real-time benefits checks capabilities that inform prescribers and patients about price differences at the point of prescribing are necessary to accurately guide selection of lower-cost formulations.

INTRODUCTION

High drug prices are a key policy concern.^{2,3} Rising prices not only contribute to high health care spending, but also place undue financial burden on patients in the form of out-of-pocket costs.³ High out-of-pocket costs create barriers to medication adherence which in turn contribute to worse health.^{4,5} In response, policymakers, payers, and providers are pursuing efforts to encourage prescribing of lower-cost alternatives when available and clinically appropriate, through various strategies including price transparency and electronic health record alerts.^{6,7}

For drugs that are available in multiple formulations, switching to a lower-cost formulation could offer an opportunity to reduce drug spending through the use of clinically-appropriate substitutes. The opportunity to save by switching formulations will be greater for medications with larger price differences between formulations and for medications that are currently more frequently prescribed in the higher-cost formulation. We examine medications available in pairs of formulations that are typically clinically substitutable: capsule versus tablet (separately for non-extended release and extended release medications) and ointment versus cream. We estimated the price differences between formulations across drugs after adjusting for the quantity ordered and the patient's insurer. We measured the proportion of orders that were for the more expensive formulation despite a lower-cost formulation being available. We also calculated the opportunity for savings from shifting to a lower-cost formulation based on existing prescribing practices.

METHODS

Study Data

We use data from Gemini Health which offers real-time benefits check technology to health care systems. Our data contained information on medication orders initiated by prescribers in California, Minnesota, and New Jersey to patients covered by any of 3 large private insurers during the month of August 2019. For each medication order initiated, our data contained the drug (defined as a medication in a specific concentration; e.g., Dexamphetamine-30mg), the formulation, quantity (corresponds to the number of units in the case of tablets and capsules or volume in the case of ointment and creams), the patient's insurer, the pharmacy to which the order was sent, and the insurer- and pharmacy-specific negotiated price for the drug (inclusive of the amount to be paid by the insurer and the patient). For each medication order initiated, our data also contained the same information for up to 3 available lower-cost alternatives presented by Gemini Health's technology to the prescriber.

Sample

We focused analyses on medications available in multiple formulations. Specifically, we separately examined medications in the following categories: 1) non-extended release medications available in tablet and capsule formulations; 2) extended release medications available in tablet and capsule formulations; and 3) medications available in ointment and cream formulations. We focused on these three categories, because our data contained a relatively high volume of medications available in both formulations within each of these pairs. Moreover, medications available in either of these formulations are potentially clinically substitutable, increasing the likelihood that prescribers could save by switching to the lower-cost formulation without compromising clinical quality. We excluded a small number observations with negotiated price information that is missing or equal to zero on the basis that they were data errors.

Outcomes

Our first outcome was the negotiated price paid for the drug, which was defined as the sum of all payments to be made by the insurer and the patient (inclusive of any deductible, copay, and coinsurance owed) for the medication prescribed. We also measured the proportion of medication orders initiated for the more expensive formulation and the savings that would have resulted if all orders placed for the higher-cost formulation had instead been placed for the lower-cost formulation for the same medication.

Statistical analysis

Medication price differences by formulation

To estimate the within-drug price difference between formulations, we estimated the following model using linear regression for each of the 3 medication categories of interest:

$$\begin{aligned} \text{Log}(\text{price}_{ndi}) = & \beta_0 + \\ & \gamma \mathbb{1}(\text{Formulation: Capsule, ERCapsule, Cream} = 1)_{ndip} * \alpha_d + \beta_1 \text{Log}(\text{Quantity}_{ndi}) + \\ & \beta_1 \text{Log}(\text{DaysSupply}_{ndi}) + \alpha_d + \alpha_i + e_{ndi} \end{aligned}$$

where price_{ndip} denotes the negotiated price for observation n for medication d negotiated by insurer i , $\mathbb{1}(\text{Formulation: Capsule, ERCapsule, Cream} = 1)_{ndi}$ indicates whether observation n is an order for a capsule (versus tablet), ER capsule (versus ER tablet), and cream (versus ointment), Quantity_{ndi} denotes the quantity prescribed, DaysSupply_{ndi} denotes the days supply ordered, α_d denotes a vector of drug fixed effects, α_i denotes a vector of insurer fixed effects, and e_{ndi} is a random error term. The term $\mathbb{1}(\text{Formulation: Capsule, ERCapsule, Cream} = 1)_{ndi}$ denotes a vector of interactions between the formulation and drug-specific fixed effects. The coefficient estimates for each interaction term represent the average relative price difference between formulations available

for medication d . For each drug, we plotted the estimated coefficients and 95% confidence intervals, based on robust standard errors clustered at the insurer level.⁸ In these analyses, we combined price information from initiated orders and suggested alternatives to maximize the number of price observations in our data. We logged our outcome, so we could estimate relative (percentage) rather than absolute price differences and to attenuate bias from outliers in our data. In secondary analyses, we stratified by 2 insurers which accounted for the majority of observations in our data to examine the generalizability of our findings across insurers. We additionally compared pharmacy-specific medication prices across formulations to examine the extent to which price differences between formulations are consistent across pharmacies.

Calculating the opportunity for savings from switching to the lower-cost formulation

We used information on medication orders initiated to measure the proportion of observations for which the more expensive formulation was ordered and to simulate the potential savings that would have resulted if these orders had instead been initiated for the less expensive formulation. We first assigned a unit-level price to each medication-formulation combination, calculated as the total negotiated price divided by the quantity averaged across all observations in our data. (In secondary analyses, we assigned the median price instead of the mean in case our main results were sensitive to outlier observations.) We counted the proportion of orders that were initiated for the more expensive formulation based on the calculated quantity-adjusted prices.

To estimate the potential savings, we calculated the minimum potential spend for each medication order initiated, by multiplying the quantity ordered with the unit-level price assigned to the lower cost formulation. We estimated the total spend for each order by multiplying the quantity ordered with the unit-level price for the formulation that was actually ordered. The

difference between the total spend and the minimum spend divided by the total spend was the opportunity for savings from switching. We summed the opportunity for savings across orders for each medication. For analyses on the proportion of orders placed for the more expensive formulation and the opportunity for savings measurement, we required our data to contain at least 5 initiated orders for a medication to be included.

RESULTS

Our sample contains 16,218 observations (inclusive of orders initiated and alternatives suggested by the Gemini Health technology) across the three categories of interest (Table 1). Of these, half were orders initiated and half were suggested alternatives. Our data contained 28 unique non-ER medications available as both tablets and capsules, 16 unique ER medications available as both tablets and capsules, and 24 unique medications available as both cream and ointment.

Figure 1 plots the estimated medication-level price difference by formulation and associated 95% confidence intervals. Among the 28 drugs available as tablets and capsules, 9 were more expensive in tablet form, 8 in capsule form, and 11 did not have statistically significant price differences by formulation (Panel A). Cephalexin-500mg had the largest estimated price difference. The mean price for cephalexin-500mg (for an order quantity of 30 units) was \$4.6 for capsules and \$194.6 for tablets, implying an unadjusted price difference between formulations of 4,130%. Our model coefficient estimate was 3.55 (p-value=0.002), which implies a 3,381% ($(\exp(3.55)-1)*100=3,381\%$) adjusted price difference.

Among the 16 ER medications available in tablet and capsule formulation, our estimates indicated that 7 were more expensive as tablets, 7 as capsules, and 2 did not have statistically significant price differences by formulation. Among ER medications, venlafaxine-75mg had the

largest price difference. The mean price for venlafaxine-75mg (30 units quantity) was \$2.5 in capsule formulation and \$140.6 in tablet formulation, yielding an unadjusted price difference of 5,524%. Adjusted estimates implied that tablets were 4,208% (estimate=3.76, $p<0.001$) more expensive than capsules.

Among the 24 drugs available as ointment and cream, 2 were more expensive as ointment, 6 as cream, and 16 did not have statistically significant price differences by formulation. Among medications more expensive as creams, mupirocin-2% had the largest price difference with creams estimated to be 2,988% (estimate=3.43, $p=0.003$) more expensive than ointments on average. The unadjusted price difference was 3,280%, with a mean price of \$165.6 in cream formulation and \$4.9 in ointment formulation (fixed at the modal quantity). Among medications that were more expensive in ointment formulations, the magnitudes of the price differences were smaller. Temovate-0.05% had the largest price difference, with ointments estimated to be 12% (estimate=-0.11, $p<0.001$) more expensive than creams, which was equivalent to the unadjusted price difference. The mean price for the cream formulation was \$121.2 and the mean price for the ointment was \$135.5 (fixed at the modal quantity).

Our secondary analyses suggest that for a given medication, the price differences between formulations was largely, though not entirely, consistent across insurers as well as pharmacies. Among medications with sufficient observations, the same formulation was estimated to be lower priced for 86% (19 out of 22) of medications available in tablet and capsule formulation, 100% (7 out of 7) of extended-release medications available in tablet and capsule formulation, and 50% (11 out of 22) of medications available in cream and ointment formulations (Table A1 in the Supplementary Appendix). Similarly, in cases in which our data contained sufficient price observations across formulations across multiple pharmacies, we found

that the same formulation was more expensive across pharmacies in most but not all cases (Figure A1).

Figure 2 plots the proportion of medication orders that were initiated for the more expensive formulation. In aggregate, the proportion of orders placed for the more expensive formulation was 31% for non-ER medications available in both tablet and capsule formulation, 25% for ER medications available in tablet and capsule formulation, and 49% for medications available as creams and ointments. There was variation in this proportion across medications. If all orders placed for the more expensive formulation had instead been placed for the lower-cost formulations, spending would have been 34% lower for non-ER medications available as tablets and capsules, 47% lower for ER medications available as tablets and capsules, and 17% lower for medications available as ointments and creams. Figure 3 presents the opportunity for savings by medication.

We find that the opportunity for savings from switching formulations stem from both large price differences between formulations as well as a high proportion of orders that are initiated for the more expensive formulation. For example, fluoxetine-20mg was estimated to have 87% opportunity for savings if all orders had been for the capsule formulation. These savings were driven by an estimated 2,722% (estimate=-3.34, p-value=0.02) higher price for the tablet over the capsule and 27% (42 out of 158) of orders that were initiated for the more expensive medication. Among extended release medications, verapamil-240mg had an estimated opportunity for savings of 79% from switching all orders to tablet, driven by estimated price differences that were substantial though smaller compared to the previous example (589%; estimate=1.93, p-value=0.008) but a greater proportion of orders placed for the more expensive formulation (62%). Our robustness analyses using the median value to assign a price to each

medication-formulation combination yielded conclusions similar to our main analyses (Figures A2 and A3).

DISCUSSION

We identify formulation as a dimension on which prices for the same medication can differ substantially, upwards of 4,000% in the case of several medications. Moreover, for 41% of orders, the same medication was available in a lower-cost formulation. Aggregating across all the medications we examined, we estimated that switching to the lower cost formulation could have lowered spending on these drugs by 24%. Our findings suggest that encouraging prescribing of lower-cost formulations could offer substantial opportunity for lowering drug spending.

Most efforts to encourage prescribing of lower-cost drugs have focused on encouraging prescribing of different medications determined to be therapeutically equivalent, prescribing in larger days supply for a quantity discount, or switching to mail-order pharmacies. However, merely switching formulations may offer a means to lower drug spending without significantly compromising clinical appropriateness, safety, or convenience. Even given mild differences in therapeutic equivalence between formulations, switching to a lower-cost formulation could reduce patient's out-of-pocket burden, and in turn, improve medication adherence and health outcomes.

However, inconsistency in which formulation was more expensive across medications highlights the necessity of decision-making tools at the point of prescribing to facilitate prescribing of lower-cost formulations, since one-size-fits all rules (e.g., always prescribe capsules when available) would not be appropriate. The value of such a decision-making tool is

further pronounced by our finding that for a given medication, the same formulation was lower cost across insurers and pharmacies in most but not all cases.

Real-time prescription benefits checks capabilities, which are increasingly being adopted by health care systems offer a means to inform clinicians about available lower-cost alternatives at the point of care. Real-time benefits checks are typically integrated into the electronic health record and provide insurer-specific cost estimates and suggest clinically-appropriate alternatives.⁷ Surescripts, a leading provider of such a capability, has reported significant growth in adoption in recent years.⁸ The Centers for Medicare and Medicaid Services has announced its intention to require every Medicare Part D plan to offer real-time pricing comparisons to prescribers within the next several years.⁹ These efforts should suggest lower-cost formulations when available as alternatives to prescribers.

Our study had several limitations. First, we could not identify the reason underlying prices differed by formulation. However, the fact that the same formulation is not consistently lower cost across all medications suggests that price differences do not reflect differences in quality or costs of production. Second, our data reflected medication orders initiated by prescribers in California, Minnesota, and New Jersey and prices negotiated by 3 insurers during a 1-month time frame. As a result, our findings may not generalize. While the specific prices may differ, we expect that our general findings that prices can differ substantially by formulation and inconsistently across medications would hold in other settings. Moreover, by using a short time-frame we avoided pricing differences that may have resulted from contract renegotiations. Third, the prices in our data exclude plan rebates, and therefore, may not reflect true price differences or potential savings that would accrue to the health plan. However, as long as such plan rebates do not vary by formulation, the relative savings should be consistent. Moreover, since out-of-

pocket costs are typically based on the pre-rebate prices, our savings are likely to be better correlated with savings as they would accrue to the patients. In the case of employer-sponsored insurance plans moreover, our prices reflect accurate prices paid since rebates typically accrue to the prescription benefit manager and not the employer. Similarly, our analyses estimated price differences and potential for savings overall and not for the patient specifically. Patient savings could be substantially lower if out-of-pocket costs do not vary to the same degree across formulations. Nonetheless, future analyses should quantify the extent to which switching formulations could result in savings to the patient specifically.

In conclusion, formulation is a dimension across which medication prices can vary substantially. Though our analyses focused on 68 medications and 3 pairs of formulations across which we had a high volume of data, similar variation is likely to exist across other formulations and medications as well. Payers, providers, and policymakers should pursue solutions to provide medication- and insurer-specific price information to facilitate selection of lower-cost formulations when available and clinically appropriate.

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Figure Legend

Figure 1. Medication-specific price difference estimates between formulation

This figure plots coefficient estimates and 95% confidence intervals corresponding to the adjusted price differences between formulations for each medication in our sample (corresponding to the interaction term between the medication fixed effects and formulation-specific indicator in our analytic model). Our model adjusted for quantity, days supply, and insurer-specific indicators. 95% confidence intervals were based on heterogeneity-robust standard errors clustered at the insurer level. By calculating $(\exp(\text{estimate})-1)*100$, the coefficient estimates can be interpreted as percentage price differences.

Panel A presents estimated price differences for medications available in both capsule and tablet formulation. Positive estimates indicate the price for the capsule is greater. Panel B presents estimated price differences for ER medications available in both capsule and tablet formulation. Positive estimates indicate the capsule price is higher. Panel C presents estimated price differences for medications available in cream and ointment formulations. Positive estimates indicate the cream price is greater.

Figure 2. Proportion of orders placed for the more expensive formulation by medication

For each medication, this figure plots the percent of medication orders initiated for the more expensive formulation (regardless of which formulation was more expensive). Panel A pertains to non-ER medications available in capsule and tablet formulation, Panel B pertains to ER medications available in capsule and tablet formulation, and the Panel C pertains to medications available in cream and ointment formulation.

Figure 3. Medication-specific opportunity for savings from switching to a lower-cost formulation

For each medication, this figure plots the simulated opportunity for savings if all orders that were initiated for the more expensive formulation had instead been placed for the less expensive formulation. Panel A pertains to non-ER medications available in capsule and tablet formulation, Panel B pertains to ER medications available in capsule and tablet formulation, and Panel C pertains to medications available in cream and ointment formulation.

Table. Descriptive statistics by medication category

	Capsule	Tablet	ER capsule	ER tablet	Cream	Ointment
No. unique drugs ¹	28	28	16	16	24	24
No. observations ²	2938	2316	970	348	5094	4552
No. orders initiated	1351	1915	224	130	2562	1907
No. alternatives suggested	1587	401	746	218	2532	2645
Quantity, mean ³	39	44	45	63	2025	3600
Days supply, mean	25	24	41	44	30	30
Price (\$), mean ⁴	15.7	43.9	12	44.6	26.9	20.9

¹A medication is defined by a unique drug-concentration combination.

²Observations include both orders initiated and alternatives suggested.

³Quantity indicates the number of units for tablet and capsule formulations and the volume for cream and ointment formulations.

⁴Price is the sum of amount to be paid by the payer and the patient inclusive of any copay, coinsurance, and deductible.

Figure 1. Medication-specific price difference estimates between formulation

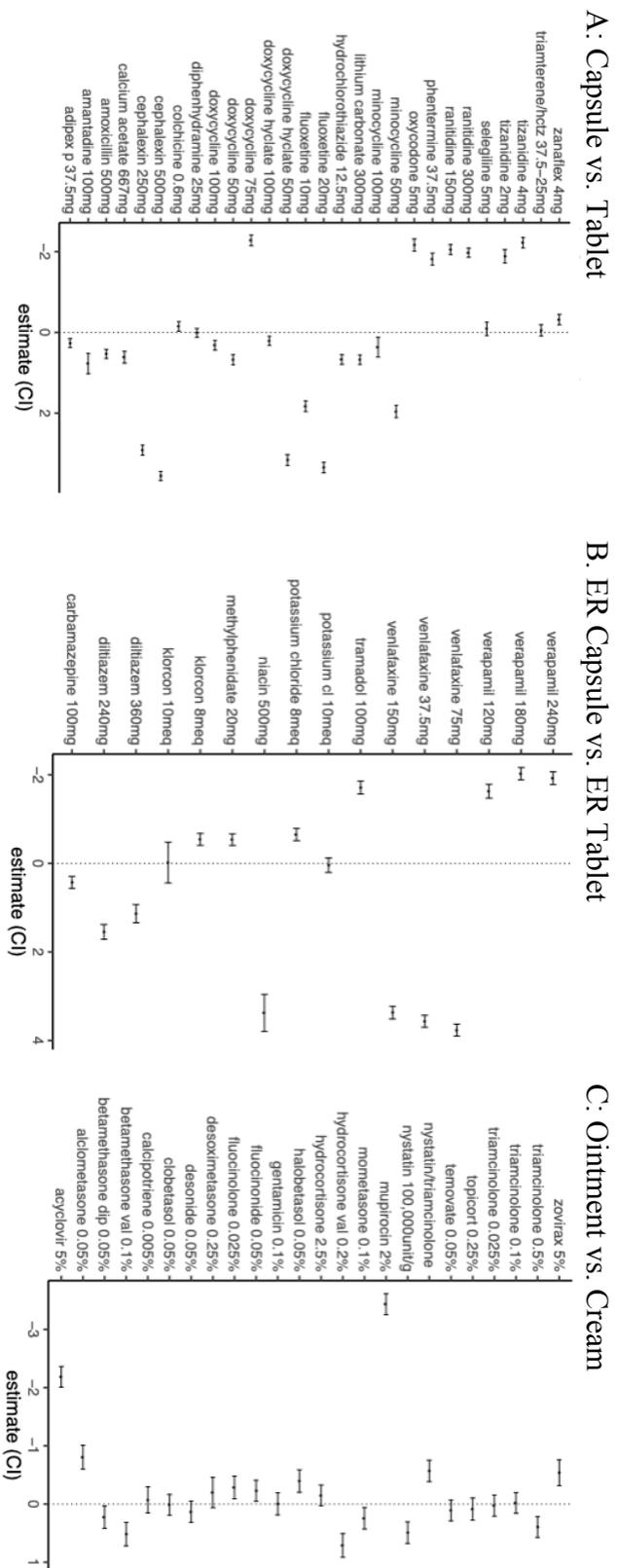


Figure 2. Proportion of orders placed for the more expensive formulation by medication

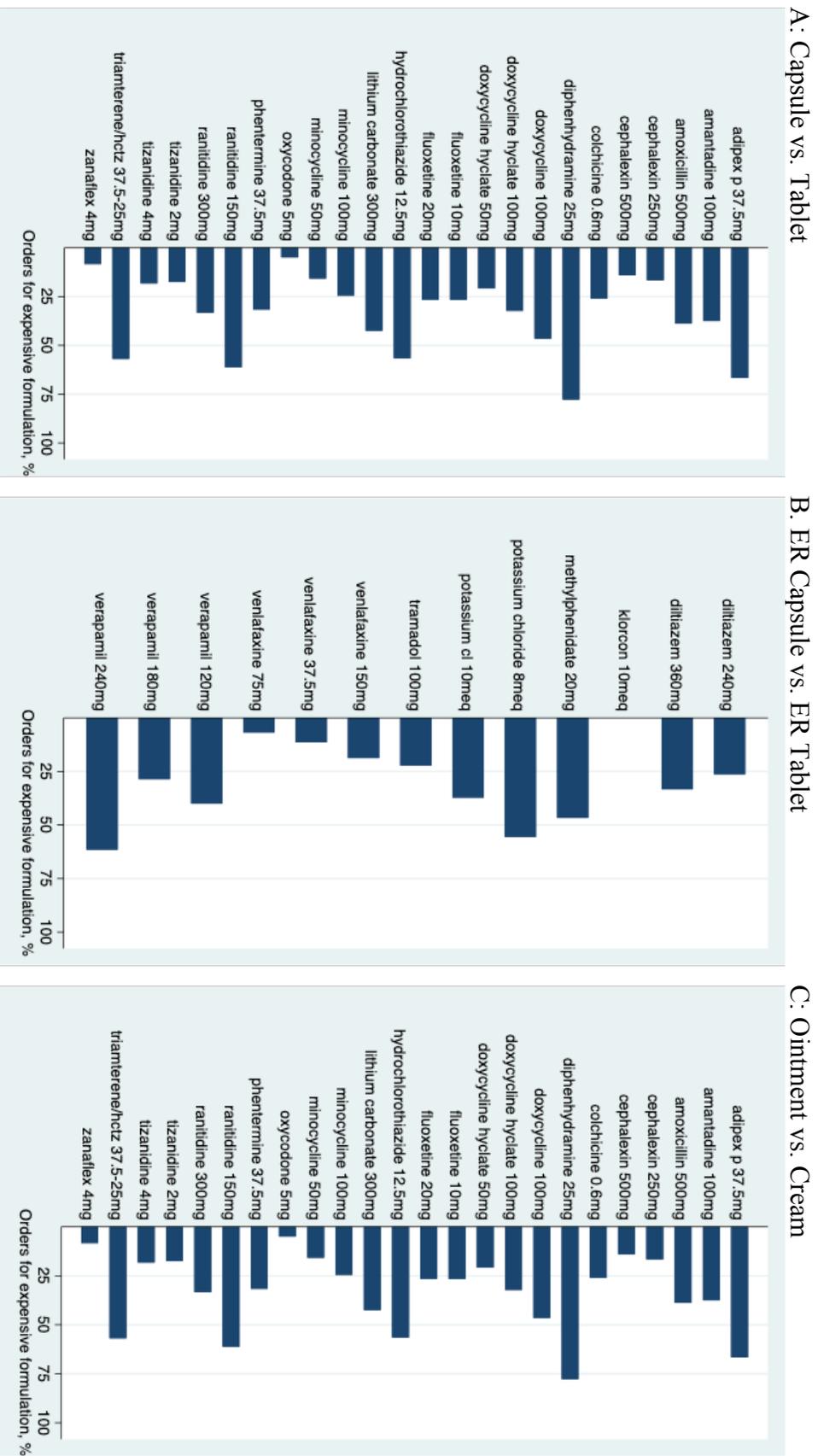


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