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PERSPECTIVE

The Costs of Drugs in Infectious Diseases: Branded, Generics, and Why We Should Care

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(See the Editorial Commentary by Kapadia and Gulick, on pages 681–4.)

While health care providers have largely turned a blind eye, the cost of health care in the US has been skyrocketing, in part as a result of rising drug prices. Patent protections and market exclusivity, while serving to incentivize targeted new drug development, have exacerbated inequitable outcomes and reduced access, sometimes fueling national epidemics. Branded drug manufacturers face few barriers to exorbitant pricing of drugs with exclusivity—as in the cases of Sovaldi, Zyvox, and Truvada. Furthermore, albendazole, pyrimethamine, and penicillin demonstrate that generic medications without patent exclusivity are not guaranteed to have durably low costs, especially where manufacturer competition is lacking. There is a way forward: through education and awareness, cost-conscious guideline development, government regulation, and market-level incentives, health care providers can collaborate to contain drug prices, curbing expenditures overall while expanding health care access to patients.

Keywords. drug costs; branded; generic; infectious diseases; HIV; hepatitis C.

INTRODUCTION

In 2016, the US spent 17.8% of its gross domestic product (GDP) on health care, while comparable developed countries spent between 8% and 12% of their GDP [1]. Despite large financial outlays, key public health outcomes in the US, including maternal (26.4/100 000) and infant mortality (5.8/100 000 live births), rank worst among developed nations, even compared to those that spend much less [1]. The US is similarly an outlier with regard to outcomes of inequity: 22% of Americans have skipped a consultation due to cost and 43% of those below average income report that their health care needs are unmet [1]. As evidence, in 2016, 45 million (18%) Americans did not fill a prescription due to high drug costs—a rate 9-fold higher than that of the UK (2%) [2]. Although the growth in government health care expenditure as well as out of pocket expenditure slowed in 2017, inequities persist [3]; while the wealthy are generally prescribed the best and newest drugs, racking up health care costs, financial barriers prevent others from receiving care or filling prescriptions at all [4].

Equally as notable as soaring expenditures is the lack of awareness and perceived lack of responsibility to control these costs among professional health care providers, in part due to a dearth of economic-conscious medical education [5]. In a random sample of nearly 3000 physicians in the American Medical Association, only 36% agreed that doctors have a major responsibility to reduce health care costs. A mere 23% of these physicians reported being aware of the costs of tests and treatments they recommend [6]. These data beg the question: has modern medical education improved cost consciousness? A survey of more than 18 000 internal medicine residents suggests the answer is no: only 46% of residents reported that they incorporate the costs of tests and treatments into clinical decisions, and an even smaller number, 24%, reported that they share the estimated costs of care with patients [7].

Fueling this lack of awareness is a scarcity of guideline recommendations that focus on cost containment. Among a series of US clinical guidelines written in 2009 or later, including those on intravascular catheter-related infections, prostate cancer, and Crohn disease, among others, few provide explicit or detailed recommendations on curbing costs, and many lack a single reference to either cost, price, or generic alternatives [8–10]. While health care expenditures soar and inequitable access persists, perpetuating poor population outcomes, physicians, governmental agencies, and clinical guideline committees have largely remained unaware of the key role they have to play.

In this report, focusing on the role of physicians, we discuss a series of drugs, both branded and generic, intentionally selected because they illustrate an important story, one of which prescribers should be more aware. To compare drug prices to one another and to illustrate price changes

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over time, we frequently refer to the average wholesale price (AWP), historically used to set reimbursement rates for pharmacies [11]. Largely related to drug monopolies and patent protections, today's era has seen drug prices soar. And, we believe that there is something we can do about it—as physicians, health care providers, and patients, health care costs should matter and creative solutions are not only feasible but necessary.

BRANDED DRUGS

Research and Development

Pharmaceutical research and development is the common justification and defense for high drug prices [12]. However, the top 5 companies with the largest spending in research and development ($12–$16 billion) in 2017 were not in pharma, but rather in the automotive, technology, and manufacturing industries. Only 5 pharmaceutical companies made the top 15 in research and development spending, with estimated expenditures ranging from $8 to $11 billion [13]. Meanwhile, estimated profit margins range from 4% to 9% for nonpharma companies but are a lopsided 17.5% for the pharmaceutical industry, calling into question the narrative that drug pricing is merely necessary to sustain research and development costs [14]. The most frequently cited estimate of the cost required to bring a new drug to market is $2.56 billion, but this figure has been criticized due to lack of study transparency (the drugs were not specified), source of data (pharma surveys), and funding (from pharmaceutical and biotechnology) [15]. Another estimate falls 10-fold lower at $110–$170 million per drug [12]. It is important to recognize that not all drug development costs are borne solely by industry; the National Institutes of Health (NIH) provided funding for each of the 210 new drugs approved by the Food and Drug Administration (FDA) between 2010 and 2016, totaling over $100 billion [16]. Not only are the true costs to industry opaque, but a 2016 report to US Congress notes, "the prices charged for drugs are unrelated to their development costs. Drug manufacturers set prices [after R and D has finished] to maximize profits" [17]. The validity of this quote is highlighted in several examples that follow.

Sovaldi: Sofosbuvir

Approximately 5.3 million Americans—and 170 million people worldwide—are infected with hepatitis C. Since its discovery in 1989, treatment has focused on poorly tolerated interferon-based therapy with sustained virologic response rates ≤10% [18, 19]. Therapy has gradually improved over time, with a major advance in 2014 in the discovery of sofosbuvir (Sovaldi) and its sister drug sofosbuvir + ledipasvir (Harvoni); these drugs have led to sustained virologic response rates—effectively cures—in over 95% of those treated.

Sofosbuvir was discovered by Emory biochemist Professor Raymond Shiniazi in his academic work funded by the NIH and Veterans Administration. In 2004, Shinazi helped to establish Pharmasset Inc., which spent about $62.4 million on the research and development of sofosbuvir (later named Sovaldi) before selling the drug to Gilead Sciences for $11.2 billion in 2012. Phase II trials of Sovaldi were funded by the NIH and phase III trials were funded by Gilead at an undisclosed cost (estimated $50–$100 million). In 2014, Gilead launched Sovaldi and Harvoni, with a 12-week treatment course in the US costing $84 000 (approximately $1000 per pill) and $94 500 ($1250 per pill), respectively. For comparison, the price of Sovaldi in developed countries outside the US range from $53 000 (UK) to $28 000 (Portugal). Estimated costs to manufacture that same course range from $68 to $136 (approximately $1.62 per pill) [20]. At the intersection of public health need, media attention, and financial hardship, the US Senate Committee on Finance published a 2015 report indicating that $1.3 billion was spent by Medicaid on the drug in 2014, with just 16 281 (2.4%) HCV-infected Medicaid enrollees treated [19]. As new competitors entered the market, prices have more recently fallen [19]; as of 2018, treatment options for HCV cost as low as $55 700 for a 12-week course [21].

Zyvox: Linezolid

Launched in 2000, linezolid is an antibiotic that acts against resistant gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant pneumococci, macrolide-resistant streptococci, and vancomycin-resistant enterococci (VRE). A review of the 9 clinical trials (3144 total participants) comparing linezolid and vancomycin for soft tissue infections found that those in the linezolid group had significantly better clinical (relative risk [RR] 1.09; 95% confidence interval [CI], 1.03–1.16) and microbiological cure rates (RR, 1.08; 95% CI, 1.01–1.16) without a significant difference in all-cause mortality [22]. In 2004, there were 3 drugs on the market to treat VRE: daptomycin, linezolid, and quinupristin/dalfopristin. Daily costs for each ranged from $72 to $255 [23]. Linezolid (Zyvox) costs fell in the low end of that range ($100 per day, $50 per pill) but, among the 3, linezolid is the only orally available option; as such, a 2-week outpatient course of Zyvox carried a $1400 sticker-shocking price tag at the pharmacy counter. Justifying the high drug price were a series of cost-effectiveness analyses demonstrating that linezolid—when compared to many alternatives—was cost-effective or even cost-saving, results that were attributable to similar treatment outcomes and fewer days of hospitalization [24]. Nevertheless, these studies were carried out from a US-payer perspective and neglected to address the challenges of individual patient affordability. With exorbitant prices, Pfizer's revenue for Zyvox skyrocketed in the early 2000s, surpassing $1 billion annually by 2008 [25]. When the patent on Zyvox expired in 2015, linezolid became available generically in the US for $138 for a 2-week course (approximately $5 per pill) [26]. Generic competition has recently caused Pfizer's profits on Zyvox to plummet, with their 2017 financial report citing a revenue of $281 million [27].

Truvada: Tenofovir Disoproxil/Emtricitabine

Over time, the AWPs of fifrst-line antiretroviral regimens have dramatically

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increased over time. The AWPs of a dolutegravir-based (DTG + tenofovir disoproxil [TDF]/ emtricitabine [FTC]) and elvitegravir-based (EVG/cobicistat/ TDF/FTC) regimens, both of which have been Department of Health and Human Services first-line treatment recommendations since 2014, have increased 36% and 26% over the last 5 years. Truvada (TDF/ lamivudine) itself has increased 2.5-fold in price since its FDA-approval in August 2004, now costing approximately $20 000 per year [28]. Yet, Truvada is available internationally through the President's Emergency Plan for AIDS Relief and the Clinton Health Access Initiative at $57 per year—a helpful benchmark for what the drug costs at most to produce [29]. As the only drug combination FDA approved in the US for HIV preexposure prophylaxis (PrEP), Truvada is indicated for approximately 1 million people in the US at high risk of acquiring HIV; less than 20% are receiving it [30, 31]. Using a state-based calculation of the "PrEP-to-need ratio" (the number of PrEP prescriptions divided by the number of new HIV diagnoses), Siegler et al demonstrated clear demographic disparities in the US—states with the poorest access lie in the epidemic-ridden southeast [32]. While some have argued that PrEP access is limited by drug costs [30, 32], a recent paper from the Centers for Disease Control and Prevention suggests that <1% of those with indications for PrEP are in need of financial assistance [33]; many patients are otherwise covered by industry-sponsored medication assistance programs. Further, PrEP was not recommended until 2018 by the United States Preventive Services Task Force [34]. Nevertheless, if Truvada's cousin Descovy (tenofovir alafenamide [TAF]/emtricitabine) materializes as another option for PrEP (phase III trial data anticipated in 2019), further cost issues will emerge. Truvada will soon be generically available and cheaper, though it will no longer bear industry-sponsored assistance. As Descovy contains TAF, it will likely have similar efficacy and lower toxicity than Truvada [35]; however, it may carry much higher on-the-book drug prices. Taking into account its improved toxicity profile, a cost-effectiveness analysis demonstrated that in order for Descovy to be economically attractive in comparison to the expected much cheaper generic lamivudine/ tenofovir disoproxil fumarate, Descovy would have to be priced below Truvada's current branded price [35]. Ironically, with industry-sponsored assistance, Descovy could perversely become more patient accessible.

GENERIC DRUGS

The FDA defines a generic drug as a "medication created to be the same as an existing approved brand-name drug in dosage form, safety, strength, route of administration, quality and performance characteristics" [36]. Cost benefits associated with generic use are not immediate after a drug comes off patent. Like branded drugs, generic drugs require generic market competition before prices fall; by 2 to 3 years after loss of exclusivity protection, generic drug prices generally decrease by 60%–70% compared to their branded equivalents [37]. Sustained market competition is essential to keep prices low, even for very old unpatented drugs. In one analysis of over 1000 generic drugs, lack of competition and price hikes were clearly associated; drugs with monopolies averaged nearly a 50% price hike over a 5-year horizon [38]. In another study of over 1400 Medicare Part D generic drugs, 300 (21%) had one price hike of at least 100% between 2010 and 2015 [39].

Albendazole

Albendazole, an unpatented antiparasitic medication, is a well-known case in which loss of generic competition fueled steep and rapid price hikes. In 2010, its AWP per dose was a mere $5.92; by 2013, the price had skyrocketed 1900% to $119.58 per dose. Until 2010, GlaxoSmithKline, the manufacturer of albendazole, shared the market with Teva Pharmaceuticals, which produced the only comparable, therapeutically equivalent drug, mebendazole. Between 2010 and 2011, the market transformed: in October 2010, GlaxoSmithKline sold their US marketing rights for albendazole to Amedra Pharmaceuticals. Exactly a year later, Teva Pharmaceuticals ceased to manufacture mebendazole, giving Amedra an antiparasitic monopoly. The price of albendazole quickly soared, as did government expenditure on the drug. Before 2012, Medicaid spending on albendazole and mebendazole combined was less than $500 000. By the last quarter of 2014, spending on albendazole alone quintupled to nearly $2.5 million [40].

Pyrimethamine (Daraprim)

Pyrimethamine, a 60-year-old, unpatented drug used for treating toxoplasmosis, is yet another case of a generic drug that saw a sudden, massive price hike. For years, pyrimethamine sold for $13.50 per tablet and reportedly cost $1 per pill to make [41]. In 2015, Turing purchased the rights to the drug. When Turing took over, its CEO, Martin Shkreli, immediately raised the price to $750, an unprecedented 5000% increase [42]. Despite widespread controversy over the price hike—and Shkreli serving a 7-year sentence for securities fraud—in 2018, Daraprim still sells for over $750 a pill, now under the company's new name, Vyera Pharmaceuticals.

Penicillin

Penicillin was the first antibiotic—discovered in 1928 by Alexander Fleming—and had previously been widely available, domestically and internationally. A treatment course in the developing world today costs pennies [43].

Syphilis is a reemerging epidemic with a more than 2-fold increase in cases over the last 15 years. Over 88 000 syphilis cases were reported in 2016, a number that has not been witnessed in this country for nearly 25 years [44]. As the standard of care therapy for syphilis, penicillin supply and affordability are essential. Yet, the uptick in syphilis cases may have been in part perpetuated by a shortage of penicillin due to a 2-year manufacturing delay that began

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in 2016 [43]. Among the reasons for the shortage was a highly consolidated market, leading to a sole US manufacturer (Pfizer) and thus a lack of alternative supply when single-manufacturer delays occurred. Moreover, because penicillin is off patent and exhibits low profit margins, expanded manufacturing by other companies is an unattractive business proposition [43]. And a drug shortage often portends rising drug prices. According to an analysis of over 900 drugs that experienced a shortage between 2015 and 2016, prices increased by an average of 16% in the 11 months following the shortage, twice the expected rate; prices of drugs that had less than 3 manufactures increased an average of 27% during the same period [45]. While reports claim the penicillin delay was resolved as of May 2018, anecdotes of stock outs have reemerged in late 2018 (HIV Medicine Association,personal communication, 12 October2018).

Meanwhile, county health departments have documented that prices for benzathine penicillin have increased over 230% from 2015 to 2018, and discussions with Pfizer indicate more increases are forthcoming (Stanislaus County, CA, personalcommunication, 12 October 2018). Accounting for 2016 syphilis cases and treatment costs, penicillin likely resulted in approximately $15–$20 million in revenue, approximately 0.04% of Pfizer's $52.8 billion total revenue in that year [27].

A WAY FORWARD

Despite the aforementioned examples, high prices sometimes result in good value. Between 1990 and 2010, large pharma essentially abandoned new antibiotic development. The number of companies researching antibiotics dropped from 18 to 4; the number of newly approved antibiotics decreased from 16 to 1; and rates of MRSA, VRE, and fluoroquinolone-resistant pseudomonas were on the rise. In response to the threat of resistant organisms, Senator Henry Waxman (D-CA) proposed the Generating Antibiotic Incentives Now (GAIN) Provision, signed into law in 2012. The GAIN Provision provides for new antibiotics fast-track designation, priority review, and a 5-year extension to market exclusivity, serving to increase profits and promote development. The provision has worked: over 10 antibiotics focused on resistant organisms have been approved since 2010 [46].

As research and development is incentivized, providers must work in parallel to decrease spending. One straightforward mechanism of reducing costs is through education and awareness. Currently, emphasis on economic efficiency is often focused on decreasing hospital length of stay, but this often leads to a "shot-gun" approach to diagnostics and treatment and thus deters cost savings in these arenas. While this tactic may be financially lucrative, it leads to poor diagnostic and therapeutic stewardship. Clinical programs—from the level of student through faculty—should incorporate didactic sessions around costs into their curricula. Value rounds, where a clinic inpatient bill is reviewed, could help bring attention to cost issues in day-to-day practice. Once informed, prescribing patterns could well change toward cost-conscious (and cost-saving) trends. For example, a recent retrospective analysis of Medicare Part D data from 2011–2016 analyzed 29 branded single-tablet regimens (STRs) where generic constituents were available and might have been prescribed for independent purchase. For all 29 STRs over a 6-year period, a switch to generics could have saved over $2 billion [47]. Moreover, while data support an adherence advantage of STRs over multitablet regimens (MTRs) when taken several times a day, recent studies have shown a slim to nonsignificant clinical difference in STRs compared to once-a-day MTRs [48].

Second, we must encourage the guideline convening agencies—including those in our societies—to include costs in the discussion. Because clinicians look to these guidelines, which most often lack mention of pricing, as a critical resource to inform and influence their care, costs are infrequently included in the care calculus.

Moreover, we should embrace opportunities for cost containment at the market level. The recently launched United Healthcare plan, "My ScriptRewards," is one such program. Under this plan, the company offers a $500 annual health care debit to its members living with HIV who switch to a Cimduo (lamivudine/tenofovir-disoproxil fumarate) + Isentress or Tivicay regimen, a cheaper partly generic alternative. Some have frowned upon this program, suggesting it bribes beneficiaries toward lesser and more toxic regimens and limits provider autonomy to optimize treatment choices. Of course, these switches will require careful consideration of adherence and comorbidities (ie, those that may be associated with aging populations) as well as important collaborations between providers and patients. However, if conducted properly, this program might be the first motivational step to shift market share away from expensive drugs; if other companies follow, branded drug prices may finally stabilize as these drugs are forced into competition with the generic market. If the United Healthcare program can create results while delivering some of the cost savings back to patients, perhaps it should be lauded rather than criticized.

Finally, although this piece focuses on the role of physicians and guideline agencies, the government must play a more active role in cost containment. Our system is unique among resource-rich countries in leaving public health outcomes related to drug costs to the discretion of the markets [4]. No government regulation, legal restriction, nor pressure from a public insurer prevented the exorbitant price increases we have described; we believe they should have.

CONCLUSIONS

Consumers, payers, and producers of health care—providers, patients, societies, governmental agencies, and insurance companies—collectively bear the

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responsibility for health care and prescription drug costs. Drug costs have soared, affordability has diminished, and patients have suffered through lack of access and poorer clinical outcomes. Branded drugs offer opportunity for enormous profit, only some of which is arguably justified. Older, generic drugs can also lead to massive profit opportunities when there is limited market competition. In particular, practices that invoke vulnerable populations or limit epidemic control should motivate our collective voices and public action. As cost savings are achieved, an obvious question comes to the forefront: how can we best ensure these additional funds are reinvested in health-centric causes, perhaps those that also help curb inequitable outcomes? Now is the time to mobilize one another and our societies toward change, as current drug pricing trends are simply no longer sustainable.

Notes

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