COMMENTARY

The High Cost of Diabetes Drugs: Disparate Impact on the Most Vulnerable Patients

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> The arc of the moral universe is long, but it bends toward justice.
>
> —Martin Luther King, Jr.

Diabetes exacts a high cost in human suffering, including increased burdens of cardiovascular disease, blindness, end-stage kidney disease, and amputations. Landmark clinical trials have demonstrated the value of intensive pharmacotherapy to delay or prevent chronic complications of diabetes (1–6). Over the past decade, clinical trials demonstrated that several sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists decrease the risks of major adverse cardiovascular events, hospitalization for heart failure, and progression of diabetic kidney disease (7–12). In this issue of *Diabetes Care*, Zhou et al. (13) estimate the economic cost of glucose-lowering drugs at $57.6 billion per year in the U.S. in 2015–2017 (~15–20% of the estimated annual cost for all prescription drugs in the U.S.). At a human level, the financial burden has a devastating impact on people without health insurance and people whose insurance imposes high deductibles—the people least able to afford the high cost of diabetes drugs. Thus, the high cost of diabetes drugs has important implications for both public policy and social justice.

Zhou et al. (13) obtained data from the Medical Expenditure Panel Survey, a nationally representative survey for the civilian noninstitutionalized population in the U.S. National spending on glucose-lowering drugs was estimated by extrapolating to the entire U.S. population. The authors estimated that total national spending on glucose-lowering medications increased by 240% (from $16.9 to $57.6 billion per year expressed in 2017 dollars) in 2015–2017 compared with 2005–2007. Over the same time period, the authors estimated a 38% increase in the number of people using glucose-lowering drugs (from 15.3 to 21.1 million) and a 147% increase in the average annual cost per user (from $1,106 to $2,727). Further analysis revealed thought-provoking differences among different classes of diabetes drugs, with the largest increases in spending on insulins (+610%) and "newer" (currently proprietary) drugs (+1,730%). In contrast, spending on "older" (currently generic) drugs actually decreased (−80%), while spending on metformin changed relatively little (+11%) over the course of the decade.

Despite the attention-grabbing nature of these estimates, the simplified analysis (13) does not do justice to this extremely complicated topic. Several critical factors were not adequately taken into account:

Rebates and discounts. Insulin provides an instructive case study of the major impact of rebates and discounts (14). Working on behalf of health plans and insurance companies, pharmacy benefit managers (PBMs) often negotiate discounted prices that are below a drug's list price (Fig. 1*A*). Similarly, PBMs often require drug manufacturers to pay rebates in exchange for favorable placement of their drugs in the PBM's formulary. Typically, the PBM retains a portion of the rebate but passes most of the payment to the health plan or the insurance company. In a different context, such rebates might be viewed as "kickbacks" or "pay-to-play" arrangements, but they seem to be legal in this context. Although the size of rebates is often shrouded in secrecy, Novo Nordisk disclosed that sales rebates amounted to 59% of gross sales in the U.S. in 2016 (15). Discounts and rebates were much smaller in 2007 with the net price being approximately the same as the list price. The net price for insulin increased by ~57% between 2007 and 2016 versus a ~252% increase in the list price (Fig. 1*B*) (14,16). This translates into compound annual growth rates (CAGR) of ~5% for net price and ~15% for list price. The list price exaggerates the actual aggregate cost of paying for insulin, which is more accurately reflected by the net price. Viewed through the lens of macroeconomics, a 5% CAGR is far more manageable than a 15% CAGR. Nevertheless, it is

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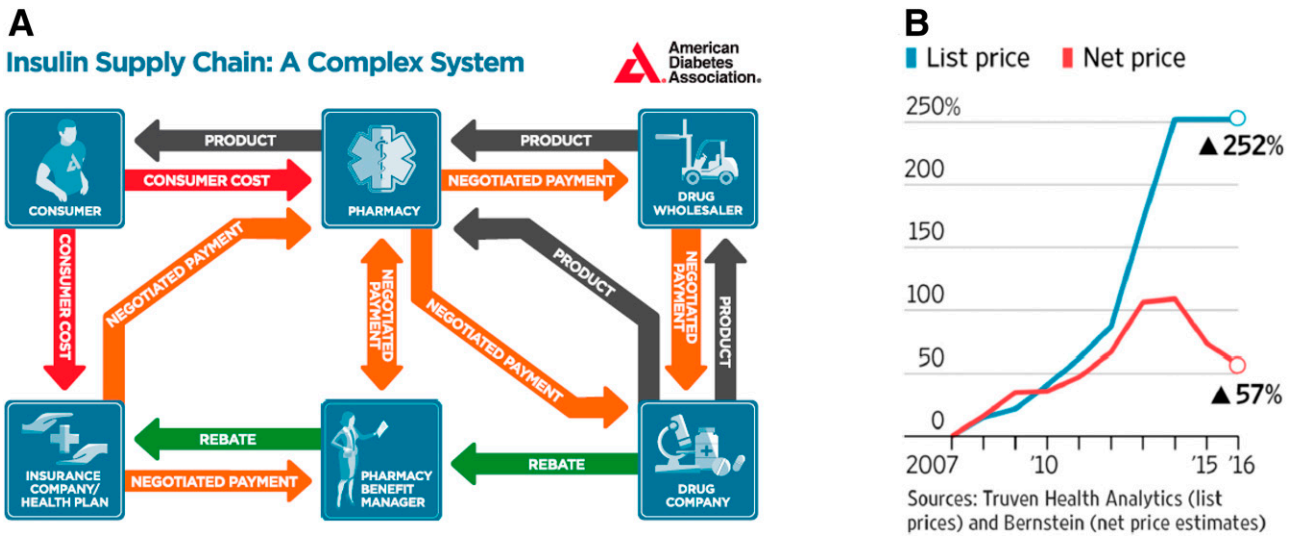

Figure 1—Impact of rebates. Panel *A* illustrates the complex supply chain for a drug such as insulin. PBMs require manufacturers to pay rebates in exchange for favorable placement of their drug in the PBM's formulary. While the PBM retains a portion of the rebate, a substantial portion is paid to the health plan or insurance company, thereby decreasing the net cost of the drug paid by that health plan/insurance company. Panel *B* illustrates the impact of rebates on price paid for insulin during the decade between 2007 and 2016. While the list price has increased by 252% throughout the entire decade, the net price (equal to the list price minus rebates and discounts) has risen by only 57% over the entire time period and actually decreased between 2014 and 2016. The figures are reproduced with permission from Cefalu et al. (14).

critical to emphasize that uninsured patients are required to pay the full list price and do not benefit from rebates or discounts. It is tragic that the present system has a devastating impact on those patients who are least able to afford insulin's rapidly increasing gross price. As discussed elsewhere (14), the rapidly increasing gross price of insulin is driven to a large extent by the actions of PBMs who have demanded increasingly large rebates and discounts since ~2013.

Losses of marketing exclusivity. The category of "older" drugs included drugs that were marketed as relatively high-priced proprietary drugs in 2005–2007 but became generic in 2015–2017: α-glucosidase inhibitors and thiazolidinediones. Losses of exclusivity likely accounted for the substantial decrease in annual cost per user (i.e., from $803 to $208) for these "older" drugs. Fortunately for patients, several drugs that Zhou et al. (13) classify as "newer" (e.g., dipeptidyl peptidase 4 [DPP-4] inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists) will become generic in the not-too-distant future, which will trigger substantial decreases in their prices. For example, according to a 10-K filing with the Securities and Exchange Commission in 2013 (17), U.S. patents on composition of matter for dapagliflozin and saxagliptin will expire in October 2020 and July 2023, respectively. Thus, generic DPP-4 inhibitors and SGLT2 inhibitors will likely be available within a few years. While the cost per user for "newer" glucose-lowering drugs increased dramatically (+178%) over the decade from 2005–2007 through 2015–2017, one can anticipate a comparably dramatic decrease in cost per user when DPP-4 inhibitors and SGLT2 inhibitors become generic.

New drug approvals. In 2005–2007, only two of the "newer" drugs were widely used: sitagliptin and short-acting exenatide. Liraglutide, which was approved in 2010, has a more attractive clinical profile than short-acting exenatide: greater glucose-lowering effect, once-a-day dosing, and decreased risk of major adverse cardiovascular events (9,18). Liraglutide's greatly improved clinical profile was a major driver of increased spending for the GLP-1 receptor agonist class of drugs in 2015–2017 versus 2005–2007. Four DPP-4 inhibitors (sitagliptin, saxagliptin, alogliptin, and linagliptin) and three SGLT2 inhibitors were available in 2015–2017. SGLT2 inhibitors have attractive clinical profiles, including weight loss, no intrinsic risk of hypoglycemia, and protection against cardiovascular and renal complications of diabetes. The compelling clinical benefits of these "newer" drugs drove the dramatic increase (+558%) in the number of users. From a clinical and humanistic perspective, these "newer" drugs provide significantly improved benefits to people with type 2 diabetes—even if they also led to increased spending.

Differential pricing at an international level. Zhou et al. (13) point out that prices for proprietary drugs are substantially higher in the U.S. as compared with other countries with similarly high per capita incomes. Unlike the U.S., many countries implement strict regulations to limit how much a manufacturer can charge for its drugs. From a microeconomics perspective, this type of behavior resembles a "perfectly discriminating monopolist" who charges different prices to different customers—with customers each paying the maximum price they are willing to pay. This is only possible because people in the U.S. are legally forbidden to buy drugs in other countries and import them back into the U.S. How can companies afford to sell drugs at lower prices outside the U.S.? In order to make a profit, companies must sell drugs for prices that exceed their costs. However, companies' costs fall into several categories. For example, companies have marginal costs to manufacture, sell, and distribute drugs. So long as companies receive payments that exceed these marginal costs, it can be profitable in the short-term for the company to make the sale. This is the situation in many countries outside the U.S. However, in order to achieve long-term profitability, companies must find a way to recoup "sunk"

costs associated with the cost of research and development that created the innovative drug in the first place. The high cost of drugs in the U.S. contributes critically to companies' ability to pay the cost of discovering and developing innovative therapies. Understandably, the U.S. population is not universally enthusiastic about this arrangement, with the U.S. contributing disproportionately to funding pharmaceutical research and development whereas other high-income countries obtain similar benefits while paying lower prices. These complex issues remain topics for heated debate.

While Zhou et al. (13) advocate for targeted interventions to reduce medication costs for treatment of diabetes, they nevertheless acknowledge that a medication regimen should be prescribed primarily based on clinical benefits rather than cost consideration. In theory, it would be possible to decrease costs by prescribing generic sulfonylureas as the second line "add-on" drug for patients inadequately controlled by metformin. However, available "real-world" epidemiological evidence strongly suggests that the metformin-sulfonylurea combination is associated with worse outcomes as compared with combinations of metformin and newer medications such as DPP-4 inhibitors, SGLT2 inhibitors, or GLP-1 receptor agonists. Relative to the metformin-sulfonylurea combination, combinations of metformin with a "newer" drug are associated with 90–95% less risk of severe hypoglycemia, 24–49% lower risk of major adverse cardiovascular events, and 23–70% lower all-cause mortality (19). Fortunately, when generic versions of these "newer" drugs become available, this will decrease financial barriers currently blocking universal access to the standard of care for type 2 diabetes. Availability of generic versions of these drugs will help bend the arc of the moral universe toward justice.

For better or worse, the world has generally relied primarily on the for-profit private sector to discover and develop innovative therapies for disease. This implicit societal decision represents a trade-off in which the private sector provides at-risk financial investments in exchange for a period of marketing exclusivity. The pharmaceutical industry has done a good job of improving therapy for type 2 diabetes by delivering three new classes of glucose-lowering drugs. However, given the U.S. approach to financing health care, the period of marketing exclusivity is characterized by high prices and restricted access to innovative therapeutic agents. Fortunately, after they become generic, these "newer" drugs will be available at more affordable prices for essentially infinitely long periods of time in the future. Nevertheless, during the ~10–15 years of marketing exclusivity, the U.S. health care system has tolerated extreme inequities in provision of access to the best available medical care. If the U.S. wishes to promote health care equity and social justice, major changes need to be implemented.

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