Curr Diab Rep (2017) 17: 71
DOI 10.1007/s11892-017-0893-0

Why Are Diabetes Medications So Expensive and What Can Be Done to Control Their Cost?

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Published online: 24 July 2017

Abstract
Purpose of Review The purposes of this study were to describe how medication prices are established, to explain why antihyperglycemic medications have become so expensive, to show trends in expenditures for antihyperglycemic medications, and to highlight strategies to control expenditures in the USA.
Recent Findings In the U.S., pharmaceutical manufacturers set the prices for new products. Between 2002 and 2012, expenditures for antihyperglycemic medications increased from $10 billion to $22 billion. This increase was primarily driven by expenditures for insulin which increased sixfold. The increase in insulin expenditures may be attributed to several factors: the shift from inexpensive beef and pork insulins to more expensive genetically engineered human insulins and insulin analogs, dramatic price increases for the available insulins, physician prescribing practices, policies that limit payers' abilities to negotiate prices, and nontransparent negotiation of rebates and discounts.
Summary The costs of antihyperglycemic medications, especially insulin, have become a barrier to diabetes treatment. While clinical interventions to shift physician prescribing practices towards lower cost drugs may provide some relief, we will ultimately need policy interventions such as more stringent requirements for patent exclusivity, greater transparency in medication pricing, greater opportunities for price negotiation, and outcomes-based pricing models to control the costs of antihyperglycemic medications.

Keywords Insulin · Oral antihyperglycemic medications · Cost · Medical Expenditure Panel Survey (MEPS)

This article is part of the Topical Collection on *Economics and Policy in Diabetes*

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Introduction

In 1923, insulin became commercially available in the United States (U.S.) [1]. Before then, there was no effective pharmacologic treatment for diabetes mellitus. It was not until 1956 that the first sulfonylurea, tolbutamide, became available in the U.S. Although the biguanide, phenformin, was available in the U.S. in the 1960s and 1970s, it was withdrawn from the market in 1978 because of its association with lactic acidosis. It was not until 1995 that metformin became available in the U.S. Since then, the pace of introduction of new classes of antihyperglycemic medications has been rapid [1]. The first alpha-glucosidase inhibitor was marketed in 1995, the first thiazolidinedione in 1996, and the first meglitinide in 1997. The first glucagon-like peptide-1 receptor agonist (GLP1-RA) and the first amylin agonist were marketed in 2005, and the

first dipeptidyl peptidase-4 (DPP-4) inhibitor was marketed in 2007. Two other medications, colesevelam, a bile acid sequestrant used for the treatment of hypercholesterolemia, and bromocriptine, a dopamine receptor agonist used for the treatment of hyperprolactinemia, acromegaly, and Parkinson's disease, were repurposed and approved for the treatment of type 2 diabetes in 2008 and 2009, respectively. The first sodium glucose co-transporter-2 (SGLT-2) inhibitor was marketed in 2013. Today, there are 11 classes of medications approved by the Food and Drug Administration (FDA) for the management of hyperglycemia in patients with diabetes [1].

The past century has seen dramatic changes in the formulations of insulin and a proliferation of agents within non-insulin antihyperglycemic medication classes. Each has come with a premium price. Table 1 shows the median cost of insulins calculated as the average wholesale price per 1000 units of the specified product in the U.S. in 2016. Table 2 shows the median monthly cost of maximum approved daily doses of non-insulin glucose-lowering medications in 2016. The purposes of this paper are to review how medication prices are established in the U.S.; to explain why medications used for the treatment of diabetes, and especially insulin, have become so expensive; to describe trends in total and per capita expenditures for antidiabetic medications in the U.S.; and to outline strategies to control their costs and reduce the financial burden of diabetes treatment.

How Are Medication Prices Established?

In the U.S., pharmaceutical manufacturers are permitted to set their own price for new products. New small molecule drugs manufactured through chemical synthesis automatically earn a period of exclusivity for 5 to 7 years after their launch before generic competitors equivalent to the brand-name product in dosage, strength, route of administration, quality, performance, and intended use can be sold. Manufacturers can use a number of strategies to extend this period of post-approval market exclusivity so that the median length is now 12.5 years for widely used drugs [2••]. In general, as medications move from brand to generic status, prices decrease substantially.

Table 1 Median cost of insulins in the U.S. calculated as average wholesale price per 1000 units of specified dosage form/product

Insulins	Compound(s)	Dosage form/product	Median AWP package price (min, max)*
Short-acting	Human regular	U-100 vial	$165
Intermediate-acting	Human NPH	U-100 vial	$165
		U-100 pre-filled pen	$350
Rapid-acting analogs	Lispro	U-100 vial	$306
		U-100 3-mL cartridges	$306 ($306, $379)
		U-100 pre-filled pen; U-200 pre-filled pen	$394
	Aspart	U-100 vial	$306
		U-100 3-mL cartridges	$380
		U-100 pre-filled pen	$395
	Glulisine	U-100 vial	$283
		U-100 pre-filled pen	$365
	Inhaled insulin	Inhalation cartridges	$557 ($453, $754)
Basal analogs	Glargine	U-100 vial; U-100 pre-filled pen; U-300 pre-filled pen	$298
	Detemir	U-100 vial; U-100 pre-filled pen	$323
	Degludec	U-100 pre-filled pen; U-200 pre-filled pen	$355
Pre-mixed products	NPH/regular 70/30	U-100 vial	$165
		U-100 pre-filled pen	$350
	Lispro 50/50	U-100 vial	$317
		U-100 pre-filled pen	$394
	Lispro 75/25	U-100 vial	$317
		U-100 pre-filled pen	$394
	Aspart 70/30	U-100 vial	$318
		U-100 pre-filled pen	$395

*AWP listed alone when only one product and/or price

Table 2 Median monthly costs of maximum approved daily dose of non-insulin glucose-lowering medications in the U.S.

Class	Compound(s)	Dosage strength/product (if applicable)	Median AWP (min, max)†	Maximum approved daily dose*
Biguanides	• Metformin	500 mg (IR)	$84 ($5, $94)	2000 mg
		850 mg (IR)	$108 ($5, $108)	2550 mg
		1000 mg (IR)	$86 ($4, $87)	2000 mg
		500 mg (ER)	$90 ($82, $6672)	2000 mg
		750 mg (ER)	$72 ($65, $92)	1500 mg
		1000 mg (ER)	$1028 ($1010, $7213)	2000 mg
Sulfonylureas (2nd gen)	• Glyburide	5 mg	$94 ($64, $103)	20 mg
		6 mg (micronized)	$50 ($48, $71)	12 mg (micronized)
	• Glipizide	10 mg (IR)	$74 ($67, $97)	40 mg (IR)
		10 mg (XL)	$97	20 mg (XL)
	• Glimepiride	4 mg	$74 ($71, $198)	8 mg
Meglitinides (glinides)	• Repaglinide	2 mg	$799 ($163, $878)	16 mg
	• Nateglinide	120 mg	$156	360 mg
TZDs	• Pioglitazone	45 mg	$349 ($348, $349)	45 mg
	• Rosiglitazone	4 mg	$355	8 mg
α-Glucosidase inhibitors	• Acarbose	100 mg	$104 ($104, 105)	300 mg
	• Miglitol	100 mg	$241	300 mg
DPP-4 inhibitors	• Sitagliptin	100 mg	$436	100 mg
	• Saxagliptin	5 mg	$436	5 mg
	• Linagliptin	5 mg	$428	5 mg
	• Alogliptin	25 mg	$436	25 mg
SGLT-2 inhibitors	• Canagliflozin	300 mg	$470	300 mg
	• Dapagliflozin	10 mg	$470	10 mg
	• Empagliflozin	25 mg	$470	25 mg
GLP1 receptor agonists	• Exenatide	10 μg pen	$729	20 μg
	• Exenatide (extended release)	2 mg powder for suspension OR pen	$692	2 mg**
	• Liraglutide	18 mg/3 mL pen	$831	1.8 mg
	• Albiglutide	50 mg pen	$527	50 mg**
	• Dulaglutide	1.5/0.5 mL pen	$690	1.5 mg**

ER and XL, extended release; IR, immediate release; TZD, thiozolidinedione

†Calculated for 30 day supply (AWP unit price x number of doses required to provide maximum approved daily dose x 30 days); median AWP listed alone when only one product and/or price

*Utilized to calculate median AWP (min, max); generic prices used, if available commercially

**Administered once weekly

When two generic manufacturers make a medication, the price decreases to approximately 55% of the brand-name price. When there are five generic manufacturers, the price decreases to 33%, and when there are 15 generic manufacturers, the price decreases to 13% of the brand-name price [2••]. As a result, medications which may initially appear "unaffordable" may become quite affordable over time with greater competition. For example, when metformin was first marketed in the U.S., the average wholesale price for a single 1000-mg tablet was $1.16. Today, two manufacturers market the same tablet at an average wholesale price of less than 10 cents [3].

Unfortunately, this has not been the case for the available insulin products. Unlike small molecules, new genetically engineered biologic drugs derived from human genes are protected from competition for 12 years in the U.S. For 60 years, all insulins available in the U.S. were derived from animal sources (beef and pork). In 1983, the first recombinant human insulin was approved by the FDA. In 1996, the first rapid-acting insulin analog was approved and over the next 20 years, a succession of rapid-acting, long-acting, and ultra-long-acting insulin analogs have been approved. As the newer insulin analogs have been introduced, the older formulations

have been withdrawn from the market or have been made available only in less convenient forms. For example, beef and pork insulins are no longer available in the U.S. and human regular insulins are no longer available in pen injection devices. In addition, because insulins are biological products, only "biosimilar" insulin formulations that have no clinically meaningful differences in terms of safety and effectiveness from the original biological product can be approved. In 2016, the first biosimilar version of the long-acting insulin analog, glargine, was approved by the FDA after being held up for 30 months because of a lawsuit claiming patent infringement. Even when available, biosimilars are not likely to produce the same cost savings as do generic drugs, purportedly due to the additional costs of development and the need to generate data to prove their safety and efficacy [4].

The most common justification for the high price of medications is that they are necessary to cover the manufacturers' investment in research and to pay for future drug development. In truth, there is little evidence to demonstrate an association between drug prices and the costs of research and development [2••]. Major pharmaceutical companies invest only 7 to 21% of sales into research and development [2••]. In addition, much of the research that leads to new drugs is performed in academic institutions with public (National Institutes of Health) support or in small biotechnology start-up companies funded by venture capital [5].

Trends in Expenditures for Antihyperglycemic Medications

There has been a pattern of increasing price over time for all of the available insulin products. When the first long-acting insulin analog, glargine, came to the market in May 2001, human NPH insulin was priced at $25 per 1000 unit vial and glargine was priced at $44 per 1000 unit vial. Between 2001 and 2014, there were 24 increases in the price of glargine ranging from 3 to 16%, such that by the end of 2016, the price per vial of glargine was $298. By 2016, the price of human NPH insulin had also increased to $165 per vial. Detemir, the second long-acting insulin analog to enter the U.S. market in 2006, also increased in price over time, and in parallel with the price of insulin glargine. Detemir now costs $323 per vial. The latest, very long-acting insulin analog to enter the U.S. market, insulin degludec, was introduced in 2016 at a price of $355 per 1000 unit vial (Table 1).

Data from the 2002, 2007, and 2012 Medical Expenditure Panel Survey (MEPS), the most complete source of data on the use and cost of health care in the U.S., showed a sixfold increase in expenditures for insulin among adults with diabetes ≥18 years of age, from $2.6 billion in 2002 to $15.4 billion in 2012 (Fig. 1a) [6]. Expenditures for non-insulin antihyperglycemic medications remained relatively stable at approximately $7 billion (Fig. 1a) [6]. The dramatic increase in total expenditures for insulin was due to at least four factors. The primary factors were the change in utilization from less expensive animal species and human insulins to more expensive insulin analogs and the increase in the price of all of the available insulins. The increase in the number of people treated with insulin and the increase in per-person insulin doses related to obesity and insulin resistance also contributed but to a lesser degree. Data from the MEPS showed that the annual per capita cost of insulin for those taking insulin increased almost fourfold over the 10-year period between 2002 and 2012 from $634 to $2358. In contrast, the annual per capita cost of non-insulin antihyperglycemic medications for those taking such medications decreased by 60% ($684 to $416) (Fig. 1b) [6]. More recently, an analysis using individual- and prescription-level data from the MEPS found that the average price of insulin increased by approximately 200%, from $4.34 per milliliter in 2002 to $12.92 per milliliter in 2013. The estimated expenditure per patient for insulin in the U.S. in 2013 was greater than all other antihyperglycemic medications combined [7•].

Over the same time period, total and per capita expenditures for antihypertensive medications and lipid-lowering medications decreased and were similar among those with and without diabetes (Fig. 2). The decline in total expenditures for antihypertensive and cholesterol-lowering medications was primarily due to the approval of generic preparations of the most commonly prescribed medications. Generic versions of the ACE inhibitors lisinopril and ramipril became available in 2002 and 2005, respectively, and generic versions of the calcium channel blocker amlodipine became available in 2005. Generic versions of the angiotensin-receptor blocker losartan were approved in 2010. Generic versions of the cholesterol-lowering medications simvastatin and pravastatin were approved in 2006 and generic versions of atorvastatin were approved in 2011.

Strategies to Control Medication Costs

One means to control the high cost of medications is for payers to leverage their purchasing power to negotiate lower prices [2••]. Unfortunately, public payers in the U.S. are constrained in their ability to negotiate prices. Federal law requires Medicare to provide broad medication coverage but prevents it from using its huge purchasing power to secure lower prices. State Medicaid programs are also generally required to cover all FDA-approved drugs, but are protected from price increases exceeding inflation and are entitled to receive rebates for most brand medications. In contrast, the Veterans Health Administration has broad authority to exclude products from its formulary and is entitled to rebates on those that it chooses to include. Nevertheless, these regulations constrain the ability of public payers to negotiate the lowest drug prices.

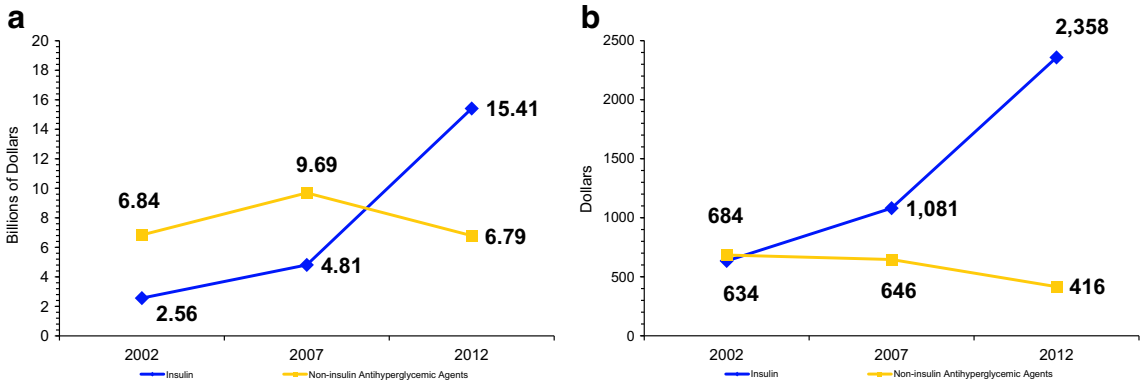

Fig. 1 Trends in total (**a**) and per capita (**b**) health care expenditures for antihyperglycemic medications among adults with diabetes taking insulin or non-insulin antihyperglycemic agents ≥ 18 years of age by medication class, U.S., 2002-2012 (adapted from: McEwen et al.) [6]

In the private payer arena, large pharmacy benefit managers (PBMs) are hired by payers to control medication costs by negotiating rebates and discounts from drug manufacturers [8•]. Unfortunately, the role of PBMs in drug pricing is not transparent. PBMs have little regulatory oversight, operate under private business contract law, and are able to keep their true costs hidden. Because part of PBM annual fees are based on the payer's spending for drugs, the PBM incentive to negotiate the lowest drug prices may not be as strong as it might otherwise be. In some cases, the PBMs may offer a "discount" of 5–10% to payers who use their mail order formulary but may have negotiated rebates from drug manufacturers that reduce their drug purchase costs by as much as 30–50% [8•]. A recent lawsuit filed in federal court in Massachusetts has charged insulin manufacturers with exploiting the country's opaque drug-pricing system in a way that benefits themselves and the PBMs to the detriment of people with diabetes [9].

Prescribing physicians may also contribute to high medication costs [2••]. It is physicians who write prescriptions, but pharmacists who fill them, and patients or their insurers who pay for them. This separation of prescribing from payment has left physicians without comprehensive knowledge of drug prices and has too often removed price from their clinical decision-making. Intensive advertising of new and expensive products to both physicians and patients has likely exacerbated this problem.

Clinical Solutions

What can be done to control the costs of antihyperglycemic medications and to reduce the financial burden of diabetes treatment? First, if not contraindicated and if tolerated, metformin, an inexpensive and effective oral antihyperglycemic medication, should be prescribed as the initial pharmacologic treatment for all patients with type 2 diabetes [10]. The use of metformin as first-line therapy for type 2 diabetes is supported by findings from the United Kingdom Prospective Diabetes Study [11] and a large meta-analysis [12].

Among the other non-insulin glucose-lowering medications available in the U.S., the sulfonylureas and thiazolidinediones represent the lowest cost options. Although both are inexpensive and effective in lowering glucose, sulfonylureas increase the risk of hypoglycemia and are associated with modest weight gain, and thiazolidinediones are associated with substantial weight

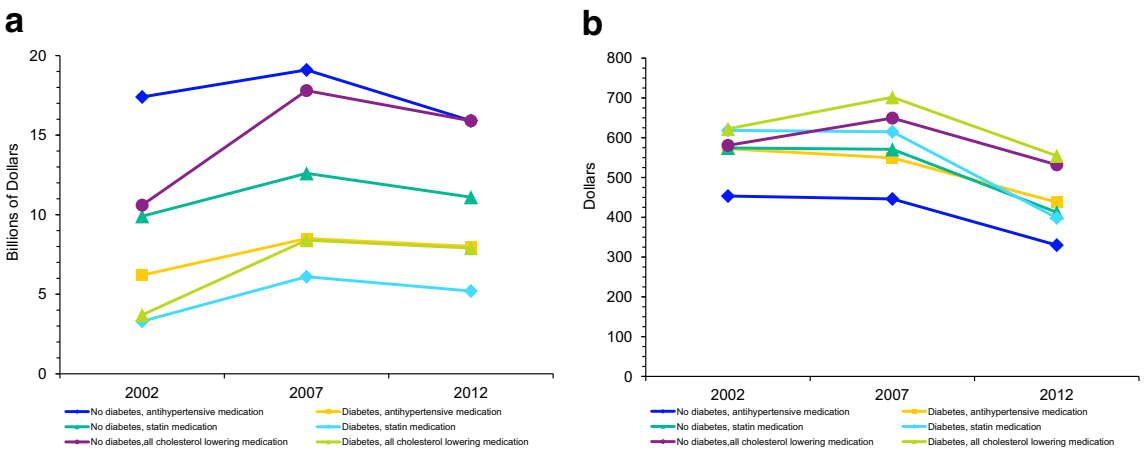

Fig. 2 Trends in total (**a**) and per capita (**b**) health care expenditures for antihypertensive and cholesterol-lowering medications among adults taking the medication designated in the legend ≥18 years of age by diabetes status and medication class, U.S., 2002–2012 (adapted from: McEwen et al.) [6]

gain, edema, heart failure, and fractures. Although more expensive and less effective, the DPP-4 inhibitors are associated with low risk of hypoglycemia, neutral impact on weight, and rare side effects. Similarly, the SGLT-2 inhibitors are associated with low risk of hypoglycemia, modest weight loss, and a reduced incidence of renal disease, major adverse cardiovascular events, and cardiovascular mortality [13, 14]. These benefits of SGLT-2 inhibitors must be weighed against their increased risk for genitourinary and urinary tract infections and the rare possibility of euglycemic diabetic ketoacidosis. The GLP1-RAs are expensive but are associated with a low risk of hypoglycemia and weight loss. In clinical trials, the GLP1-RAs have also shown cardiovascular and renal benefits but increased risk for gastrointestinal intolerance and medication discontinuation [15, 16].

Although there are many trials that have compared dual antihyperglycemic therapy with metformin therapy alone, few trials have directly compared active drugs as add-on therapy to metformin. Many clinicians are anticipating the results of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) study which is a clinical trial directly assessing the comparative effectiveness and cost-effectiveness of a sulfonylurea (glimepiride), DPP-4 inhibitor (sitagliptin), GLP1-RA (liraglutide), and basal insulin analog (glargine) as second-line therapies in combination with metformin. Unfortunately, the trial will not provide answers for at least 5 years and will not directly address the comparative effectiveness or cost-effectiveness of SGLT-2 inhibitors [17••]. Lacking clinical trial data, the American Diabetes Association [10] has recommended that the choice of second-line antihyperglycemic medication should be based on patient preferences and patient considerations including medication efficacy, risk of hypoglycemia, impact on weight, side effects, and costs. Cost-effectiveness models have suggested that some of the newer antihyperglycemic medications may be of relatively lower clinical utility because of their high cost and moderate glycemic effect. Indeed, if a patient cannot afford to fill a prescription or if the lack of financial resources represents a long-term barrier to adherence, less expensive alternatives should be prescribed.

Prescribing physicians must also carefully weigh the advantages and costs of the newer insulin analogs. Although each new analog has come with demonstrated advantages, providers must weigh whether the advantages are likely to accrue to an individual patient and whether they justify the premium price. The diabetes community should also demand greater transparency in insulin pricing to better understand the rapid increase in insulin prices, especially for the human insulins which have been on the market, unchanged, for many decades. Currently, human NPH and regular insulins are the least expensive insulin products with median average wholesale prices of $165 per vial. They are also available through Walmart Pharmacies as the Reli-On brand of human insulin at $26 per vial. In general, these inexpensive human insulins are safe and effective for the management of patients with type 2 diabetes, although the unavailability of human regular insulin in a prefilled pen is an inconvenience to patients and a potential barrier to adherence. Clinical trials have suggested that insulin analogs may be preferable for patients with type 1 diabetes, providing both more consistent mealtime coverage and a reduced incidence of nocturnal hypoglycemia, but human NPH and regular insulins remain a reasonable choice for patients with type 1 diabetes who cannot afford insulin analogs [18–20]. It should be remembered that the Diabetes Control and Complications Trial, which established the efficacy and safety of intensive insulin therapy for the prevention of diabetic microvascular and neuropathic complications in type 1 diabetes, was conducted before the introduction of long- and short-acting insulin analogs, when only animal species and human insulins were available.

Policy Solutions

Other potential strategies to address the high cost of antihyperglycemic medications in the U.S. include enforcing more stringent requirements for the award and extension of patent exclusivity, enhancing competition by ensuring timely availability of generic or biosimilar medications, and providing greater opportunities for price negotiation by both public and private payers [2••]. Some have suggested that the U.S. Federal Trade Commission or a special U.S. congressional panel look into ways to improve drug pricing transparency to help ensure that both public and private funds are being used wisely [8•]. In addition, given that the newer medications are expensive and have uncertain benefits and risks in real-world clinical practice, an outcomes-based pricing model might be considered. An outcomes-based pricing model would require that the clinical benefits of the more expensive medications be demonstrated in clinical practice to justify a premium price. This medication pricing approach would compel manufacturers and payers to share accountability for clinical outcomes and ensure that we pay for health, not for health care [21•].

Compliance with Ethical Standards

Conflict of Interest Laura N. McEwen, Sarah Stark Casagrande, and Shihchen Kuo declare that they have no conflicts of interest.

William H. Herman is a consultant for Johnson & Johnson and a member of Data Monitoring Committees for Merck Sharp & Dohme and Lexicon Pharmaceuticals.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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