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Perspective

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The U.S. Insulin Crisis — Rationing a Lifesaving Medication Discovered in the 1920s

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On January 23, 1922, insulin was successfully injected into a 14-year-old boy with severe type 1 diabetes mellitus.[1] Type 1 diabetes had been considered a universally fatal disease, with mortality approaching 100% within months after diagnosis. For their discovery of insulin, Frederick Banting and John Macleod were awarded the 1923 Nobel Prize in Physiology or Medicine.[1] The members of their team sold the patent for insulin to the University of Toronto for $1 each[1]; Banting famously stated, "Insulin does not belong to me, it belongs to the world."

Immediately after insulin's discovery, patients flocked to Toronto for what was being referred to as a "miracle substance."[1] Demand was strong but the supply was limited, which led to the initial rationing of insulin in 1923 before it was successfully mass produced by Eli Lilly and the company that later became Novo Nordisk. The price of 100 units of regular short-acting insulin was about $1 in U.S. dollars during this period (about $15 in 2019 U.S. dollars) and fell to less than 20 cents in the 1940s (about $3 in 2019 U.S. dollars) as manufacturing processes improved.

Over the past two decades, however, the price of insulin in the United States has risen substantially.[2] Today, the price of 100 units of short-acting insulin for adults without insurance is about $18. The usual dose for regular insulin is 0.5 to 1.0 units per kilogram per day (usually given before meals). Thus, for a person with type 1 diabetes who weighs 70 kg and is taking a dose of 1 unit per kilogram per day, 100 units will last less than 2 days. Most adults taking short-acting insulin also require either intermediate- or long-acting insulin, the latter of which is also quite costly (see table). Because of the high cost of insulin, Americans have reported rationing their medication,[3] which has resulted in worsening glycemic control and, in some cases, diabetic ketoacidosis and death.[4]

Approximately 90% of insulin sold in the United States is manufactured by one of three companies (Eli Lilly, Novo Nordisk, and Sanofi).[2] The rising cost of insulin in the United States can be attributed primarily to two phenomena. First, U.S. law allows pharmaceutical manufacturers to price their products at whatever level they believe the market will

Cost of Intermediate- and Long-Acting Insulin in the United States.*

Type and Brand Name	Form	Units	Cash Price ($)	Cost per 100 Units ($)
Intermediate-acting insulin				
Novolin N	NPH	1000	25	2.50
Humulin N	NPH	1000	97	9.70
Long-acting insulin				
Levemir	Detemir	1500	489	32.60
Lantus	Glargine	1500	357	23.80
Toujeo	Glargine	1350	324	24.00
Basaglar	Glargine	1500	250	16.67
Tresiba	Degludec	1800	645	35.83

* NPH denotes neutral protamine Hagedorn. Cash prices were estimated using publicly available data from GoodRx.com.

bear and to raise prices over time without limit.[2] Second, direct competition in the insulin market is lacking.[2] The most effective form of price competition for prescription drugs in the United States comes from interchangeable generic drugs made by manufacturers independent of the brand-name drug's supplier. But such products have been blocked from entering the insulin market because many current insulin products are protected by recently obtained patents covering aspects of the drug's formulation or its delivery device. Insulin manufacturers have recently begun marketing "generic" versions of their brand-name products, also known as authorized generics. Although the list price of these products is less than that of their brand-name equivalents, it remains unclear whether authorized generics will provide meaningful cost savings to patients.

Since insulin is a biologic drug, rather than a small-molecule chemical drug, there are also fewer manufacturers that have the technical capacity to synthesize it. Moreover, because of insulin's designation as a biologic, any follow-on product made by another manufacturer would require additional testing beyond what is usually required for generic drugs before approval by the Food and Drug Administration. The cost and complexity of manufacturing a follow-on insulin product means that competition will be less robust than it would be for nonbiologic drugs. When a follow-on insulin product — another manufacturer's version of Sanofi's long-acting Lantus (insulin glargine) — was formally approved in Europe in 2014 and in the United States in 2015, price reductions reported in Europe were approximately 15%.

As U.S. patients await additional follow-on insulin products that might help bring down prices, legislators have sought more immediate solutions. In May 2019, Colorado enacted a law that limits monthly copayments for insulin to $100 for people with insurance. The state's attorney general is also conducting an investigation into insulin pricing and intends to recommend additional legislative changes once it concludes. Cigna, one of the largest private health insurers in the United States, recently announced that it will limit patients' monthly copayment for insulin to $25.

On a national level, several strategies have been proposed to reduce insulin prices. The Emergency Access to Insulin Act, for example, was introduced by Senators Tina Smith (D-MN) and Kevin Cramer (R-ND) in June 2019. The bill's goal is to expand access to insulin by creating state-level insulin-assistance programs that would provide short-term supplies of insulin to patients with the greatest need. It would also impose a penalty and recurring fee on insulin manufacturers, with the goal of holding manufacturers accountable for historical price increases and preventing subsequent price increases above the rate of inflation. Finally, the bill would encourage competition by reducing market-exclusivity periods for new insulin formulations, thereby promoting the entry of follow-on alternatives.

Another bill, the Affordable Drug Manufacturing Act, introduced by Senator Elizabeth Warren (D-MA) and Representative Jan Schakowsky (D-IL) in December 2018, would have established an Office of Drug Manufacturing within the Department of Health and Human Services. The office would have been responsible for directly manufacturing — or contracting with outside entities to manufacture — essential medicines such as insulin while avoiding violating active patents. Other policies have been proposed, such as pricing insulin on the basis of international standards (i.e., international reference pricing) or

regulating the influence of pharmacy benefit managers, though these ideas haven't gained traction.

Patients have also found their own solutions to prohibitively high prices by traveling north of the border, where insulin can be purchased without a prescription. The cost of insulin in Canada varies depending on the type of insulin and the pharmacy, but a carton of insulin that costs about $300 in the United States often sells for about $20 (in U.S. dollars) in Canada, where laws regulate how much a medication can increase in price each year.[5] A formal, nationalized system of importing medications from Canada has recently been proposed in Congress in response to rising drug prices,[5] even though the authority to permit importation already exists under the Medicare Modernization Act of 2003. That law allows the importation of medications if the secretary of health and human services certifies that importation can be done safely and provide cost savings. No secretaries have taken this step, though current Secretary Alex Azar has announced that he supports the possibility of importing medications from Canada. A number of states have signed bills to allow importation of medications from Canada, though the states haven't yet received federal approval.

An audio interview with Dr. Fralick is available at NEJM.org

Of course, there isn't enough insulin in all of Canada to make large-scale importation feasible. But as solutions to the insulin-cost crisis are being considered, there is value in remembering that when the patent for insulin was first drafted in 1923, Banting and Macleod declined to be named on it. Both felt that insulin belonged to the public. Now, nearly 100 years later, insulin is inaccessible to thousands of Americans because of its high cost. If steps to improve competition continue to be insufficient in addressing this crisis, more substantial reforms to the way the United States pays for insulin will be needed.

Disclosure forms provided by the author are available at NEJM.org.

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1. Bliss M. Banting: a biography. Toronto: McClelland & Stewart, 1984.
2. Luo J, Avorn J, Kesselheim AS. Trends in Medicaid reimbursements for insulin from 1991 through 2014. JAMA Intern Med 2015;175:1681-6.
3. Herkert D, Vijayakumar P, Luo J, et al. Cost-related insulin underuse among patients with diabetes. JAMA Intern Med 2019;179:112-4.
4. Rosenthal E. When high prices mean needless death. JAMA Intern Med 2019;179:114-5.
5. Fralick M, Avorn J, Kesselheim AS. The price of crossing the border for medications. N Engl J Med 2017;377:311-3.

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Will Emergency Holds Reduce Opioid Overdose Deaths?

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The opioid overdose crisis has claimed more than 400,000 lives in the United States since 1999. As part of efforts to reduce overdose deaths and increase enrollment in treatment, lawmakers in some states are contemplating enacting or expanding emergency hold laws that permit some patients with severe substance use disorder to be involuntarily detained for short-term observation and, in some cases, treatment. A bill introduced in Rhode Island during the past two legislative sessions, for example, would allow physicians to request that a court order a 72-hour hold for inpatient treatment for a person with substance use disorder who "presents a danger or threat of danger to self, family, or others, if not treated." Similar statutes have already been enacted in other states, including Minnesota and Washington.

Emergency hold laws are modeled after, and often extensions of, existing measures that permit short-term evaluation and treatment of people in mental health crisis. Using short-term emergency holds in the context of opioid use disorder presumes that a person's risk of overdose will be mitigated by a brief, involuntary hospitalization. But the efficacy of emergency holds for substance use disorders hasn't been evaluated. Their use in this context raises ethical, legal, medical, and practical questions that merit care-