Hot topics on insulin access: pricing in the USA

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For the survey of rationing among people living with type 1 diabetes see *Diabetes Diabetes Res Clin Pract* 2021; **179:** 108996

For the Harvard Medical School study on rationing see *Ann Intern Med* 2022; **175:** 1623–26

For the **RAND Corporation analysis** see https://www.rand.org/blog/rand-review/2021/01/the-astronomical-price-of-insulin-hurts-american-families.html

For the **Human Rights Watch report** see https://www.hrw.org/report/2022/04/12/if-im-out-insulin-im-going-die/united-states-lack-regulation-fuels-crisis#_ftn126

For more on **health insurance coverage in the USA** see https://www.cdc.gov/nchs/data/nhis/earlyrelease/insur202205.pdf

It is difficult to know how many Americans ration their insulin. But it is fair to assume that the practice is widespread. In 2021, as part of the National Health Interview Survey, American adults who use insulin were asked whether they had skipped doses, taken less than they needed, or delayed purchasing the drug at any point in the previous 12 months, so as to save money. Extrapolating from the results, researchers at Harvard Medical School (Cambridge, MA, USA) concluded that one in six Americans who use insulin, corresponding to an astonishing 1·3 million people across the country, had rationed insulin in the year before the national survey.

Irl Hirsch is a Professor of Medicine at the UW Medicine Diabetes Institute at the University of Washington (Seattle, WA, USA). "Rationing insulin is not a small, insignificant thing", he pointed out. "It means high blood sugar and a greater risk of complications. Rates of diabetic ketoacidosis have been increasing in the USA, which happens when people are not getting enough insulin, and there have been documented deaths." In comments to the media in December, 2021, President Joe Biden recounted the story of a young woman called Iesha, "who was diagnosed with diabetes three days before her 21st birthday, having to choose between rent and groceries and medication…Having to ration her supply [of insulin] and feeling herself, as she says, slowly dying, she ended up in a coma".

Some studies have indicated that the prevalence of rationing might even be as high as a quarter of the 8 million or so Americans living with diabetes who are dependent on insulin. In 2018, an international survey of people with type 1 diabetes, a condition which affects over 1·5 million Americans, found that 26% of respondents from the USA had rationed insulin during the previous year. Rates of rationing for the rest of the world stood at 18%.

While there remains uncertainty over the extent of insulin rationing in the USA, there is no mystery as to the cause. The country has some of the highest drug prices in the world. A 2021 analysis by the RAND Corporation examined the cost of insulin in 33 nations of comparable income levels. The average list price of a single vial of insulin equated to US $6·94 in Australia, $7·52 in the UK, and $14·40 in Japan. In the USA, it was $98·70, almost four times as much as the next most expensive country, Chile ($21·48 per vial).

The stark differences can be attributed to the nature of the US health-care system. Drug prices are left entirely to the market. There is no equivalent of the UK's National Institute for Health and Care Excellence, for example, which undertakes cost-benefit analysis to help inform purchasing decisions by the National Health Service. The US federal health insurance programme for people aged 65 years and older, Medicare, covers around a fifth of the population and accounts for roughly a third of spending on prescription drugs. Yet, Medicare has been prohibited from negotiating prices with the pharmaceutical industry.

"In other countries, governments play a much larger role in terms of regulating health care and pharmaceuticals in general. There may be fewer choices with respect to the drugs in the formulary, but they tend to have much cheaper prices", explained Kasia Lipska, an endocrinologist at the Yale School of Medicine (New Haven, CT, USA). "Health care in the USA is profit-driven; we have multiple players in the chain from when insulin is produced to when it actually reaches the patient, and along each link in the chain, there are potential ways to make money."

The authors of a 2022 Human Rights Watch report on insulin availability in the USA wrote that the "regulatory failures have allowed for a crisis of unaffordable drug prices". They interviewed Zoe Witt, a woman with type 1 diabetes who recalled a time when she had no health insurance and so had purchase her insulin herself. Zoe was spending around $600 on two vials of (analogue) insulin each month, over a quarter of her take-home pay. She talked of rationing insulin and using it beyond its expiration date. "It was a very bleak time. I definitely remember feeling really ill", said Zoe. "You think, 'I haven't died yet.' But that whole time, you could be moments from death".

Analogue insulins account for more than 90% of insulin sales in the USA. Three firms are dominant. Eli Lilly manufactures the rapid-acting Humalog. Novo Nordisk is behind Novolog, another rapid-acting insulin, and Sanofi produces the long-acting Lantus. Since their introduction to the US market, the list prices for all three products have spiked. The Human Rights Watch report noted that from 2000–18, the inflation-adjusted cost of Novolog in the USA increased by 403%, to $289 per vial. The cost of Lantus increased by 420% from 2000–19, reaching $276 per vial. When Humalog first entered the USA in 1996, it cost $21 per vial, which translates to $35 at 2020 prices, a far cry from the $275 list price of the same year.

The rises in the list prices have slowed over the last few years. Nonetheless, there are structural reasons why it makes sense for drug companies to hike their list price for each vial of insulin, even if the majority of vials are sold at a discount. It is a complicated picture, but at the centre lie the pharmacy benefit managers who oversee the roster of medications offered by health insurance companies.

As of 2021, 91% of Americans were covered by health insurance. Two-thirds of these individuals had private coverage; the remainder were covered by public plans, predominantly Medicare and Medicaid, which provides health care for low-income Americans.

Insurance companies and employers do not tend to negotiate directly with drug manufacturers. Instead, they contract middlemen, known as pharmacy benefit managers, to negotiate on their behalf. Pharmacy benefit managers administer drug plans for more than 266 million Americans.

Drugs companies vie to have their products placed on insurance companies' formularies. In order to make their medications as attractive as possible they offer sizeable rebates on the list price. "If a manufacturer wants to inflate the value of the rebate, all they need to do is raise the list price", said Hirsch. "Take a drug listed at $100. The company sells it to the insurance company at $50, which represents a 50% rebate. But if they yank the list price to $200, they can still sell it for $50, but now the rebate is 75%". The pharmacy benefit manager retains some portion of the rebate for themselves and passes the remainder of the saving onto the insurance company, who adjust their plans accordingly.

The details of the dealings between pharmaceutical companies, pharmacy benefit managers, and insurers are commercially protected. The lack of transparency makes it difficult to define with any precision the drivers of drug pricing in the USA and the extent to which pharmacy benefit managers work to the advantage of patients. The net prices of analogue insulin—ie, the price actually received by the manufacturers—have not seen the same dramatic increases as the list prices. The list price for Novolog, for example, increased by 310% from 2003–16, whereas the net price for the drug fell by 21% over the same period. "Some would argue that if you do away with the pharmacy benefit managers, you revert to a situation where all drugs are more expensive", said Lipska. "They are inflating the list price but potentially bringing big savings to the health insurance companies. On the other hand, this is a hugely profitable industry standing in the middle of these transactions."

For many insulin-dependent patients covered by private insurance, the spiralling list prices of insulin has little bearing on their expenditure. Much depends on the deal struck by the pharmacy benefit manager, and the nature of their coverage. There are fixed fees for each prescription, known as copays, and a specified deductible that patients have to pay out of pocket each year before the insurance kicks in. For people who use insulin and have high-deductible insurance policies, the first few months of the year can entail spending thousands of dollars on insulin.

The retail prices of Humalog, Novolog, and Lantus are now well over $300 per vial in the USA. Given that patients with type 1 diabetes generally require two to three vials of insulin per month, paying out of pocket for insulin could easily imply an annual expenditure of more than $12 000. In 2021, 30 million people of all ages in the USA were uninsured and were hence liable for the full list price for any given drug. Around two-thirds of uninsured Americans who use insulin end up paying the list price.

"We know there are people who continue to struggle to afford their insulin and that not one single solution will work for everyone", stated a spokesperson for Novo Nordisk. "Regardless of insurance, there are many different situations that make insulin unaffordable or inaccessible, and people need options. We also recognize that people's situation may change throughout the year, which is why we have a number of different affordability offerings available." The spokesperson noted that around 100 000 patients receive free insulin every year from Novo Nordisk and that the company offers copay support. In 2021, Novo Nordisk assisted more than 1 million people to buy insulin.

A spokesperson for Eli Lilly said that the company was "committed to making insulin affordable for all people living with diabetes, regardless of income or insurance status", adding that "anyone is eligible to purchase their Lilly insulin prescription for $35 or less per month, regardless of the number of pens or vials they use, and whether they are uninsured or use commercial insurance, Medicaid, or are enrolled in a participating Medicare Part D plan".

Nonetheless, there are concerns that the patient access programmes offered by all three of the large insulin producing companies are underused. "If everyone can get the insulin they need, then why would we be seeing all this rationing?", asked Ned McCoy, chief executive officer of Civica, a non-profit formed by several US hospital systems and philanthropic organisations with the aim of delivering affordable medicines. Insulin access programmes are not necessarily on the radar of the primary care physicians and cardiologists who treat a lot of patients with type 2 diabetes.

"The programmes are not well publicised, and there are bureaucratic hurdles to clear. There are people who need assistance who do not qualify because their income is slightly too high", said Lipska. "Of course, I am glad these programmes exist, but they do not make a big dent for my patients."

Last year, Congress passed a bill capping out-of-pocket payments for insulin to $35 per month for individuals covered by Medicare. "The over 65s are an important proportion of the population with diabetes, but the cap does nothing for people on private plans or without insurance", commented Lipska. "It also does not do anything to bring down the price of insulin, and that is at the heart of this issue."

The US system of drug pricing is predicated on the notion that manufacturers should be able to maximise profits during the time their drug is on patent, before prices are forced down by the advent of generics. Yet insulin is now more than 100 years old, and its patent was famously sold to the University of

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Toronto (Toronto, ON, Canada) for $1. But biosimilar insulins have done little to reduce prices.

"For a generic version of a small molecule, the US Food and Drug Administration requires that you show chemical equivalence to the originator drug and file an abbreviated new drug application. For biologics, like insulin, you have to do clinical trials, collect stability data and submit the results. You have to file a biologics license application. It is a longer and more expensive process", explained McCoy. Civica plans to offer generic versions of Humalog, Novolog, and Lantus, priced at no more than $30 per vial or $55 for five pens. The prices correlate to the point at which Civica believes it will recoup its manufacturing and distribution costs. "We want our insulin to be available for everyone, and if we are able to further reduce our costs in the future, then we will drop our prices", McCoy told *The Lancet Diabetes & Endocrinology*. The goal is to launch the first generic insulin in 2024.Patients unable to afford analogue insulin might be able to switch to human insulin, which is available for around $25 per vial, although these are trickier to use than the analogue versions and require medical supervision. The Human Rights Watch report cited several examples of patients who died after moving from analogue to human insulin and noted that health-care providers were not always trained in overseeing the use of human insulin.

Several states have taken matters into their own hands and passed legislation capping the cost of insulin. Hirsch would like to see the Medicare cap extended to privately insured patients. An attempt to do so failed to pass the Senate last year. A particularly vulnerable population are those who do not meet the threshold for Medicaid coverage, whose employers do not offer health insurance, and whose income is insufficient for them to purchase coverage. Hirsch reckons that the Affordable Care Act (2010) has saved lives by allowing youngsters with type 1 diabetes to remain on their parents' insurance until the age of 26 years.

The Affordable Care Act also mandated extending Medicaid coverage to all adults whose income is up to 138% of the federal poverty line. But 11 states have still declined to adopt the expansion. "Rolling out the Medicaid expansion should be done immediately", said Hirsch. "It beggars belief that we have politicians representing states with large numbers of people living with diabetes, who are nonetheless voting against policies that would improve the lives of these people."

Building consensus in the polarised US political system is not straightforward. The legislation which included the provisions for the Medicare cap was opposed by every single Republican senator. Lipska advocates modelling exactly how much insulin rationing is costing the USA, alongside how much money could be saved by free provision of insulin or minimal copays. "If we can give Congress some figures to work with maybe they will realise what a good investment it is to ensure everyone has the insulin they need", she said. Advocates can at least count on the support of the president. In his remarks to the press of December, 2021, Biden talked of two sisters who shared insulin from the same vial. "Shame on us as a nation if we can't do better than this", he concluded.

Talha Burki