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This article was published on April 4, 2016, at NEJM.org.

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DOI: 10.1056/NEJMp1600894


# Essential Medicines in the United States — Why Access Is Diminishing

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On August 10, 2015, Turing Pharmaceuticals bought the marketing rights to pyrimethamine (Daraprim), a decades-old first-line treatment for toxoplasmosis. The price of pyrimethamine immediately increased by 5433%. Heavy scrutiny followed, and although Turing agreed to reduce the price, the drug remains prohibitively expensive for many patients. Recently, at our hospital, an immigrant patient with a new diagnosis of HIV–AIDS and toxoplasmosis couldn't receive first-line therapy because of cost: the price for 100 pills was $75,000. The patient is currently receiving second-line therapy.

Unfortunately, the highly publicized pyrimethamine acquisition is not unique. Prices have been quietly but dramatically increasing for many older, off-patent drugs. Some of these medicines are considered essential by the World Health Organization (WHO) (see Table 1). In some cases, price hikes have disproportionately affected vulnerable populations, making potentially lifesaving therapies unavailable to disadvantaged patients. It seems that a new business model has emerged: companies are acquiring drugs in niche markets where there are few or no therapeutic alternatives in order to maximize their profits. Unlike new brand-name drugs, the patents of the drugs being targeted by this model expired years ago. These companies seem to have no interest in adding value to the health care system by developing new drugs.

The increased cost of albendazole, an antiparasitic medication, is a case in point.[1] CorePharma acquired the U.S. marketing license for albendazole from GlaxoSmithKline in 2010 and subsequently sold it to a private equity group, Amedra Pharmaceuticals. Amedra then bought the only potential competitor available on the U.S. market, mebendazole, from Teva Pharmaceuticals. Since Amedra's acquisition, albendazole's average wholesale price has increased by 3299%, from $5.92 per typical daily dose in 2010 to $201.27 in 2015.[2]

Other pharmaceutical companies have also used this strategy for manipulating the market. Valeant Pharmaceuticals, a publicly traded company with 2014 revenues of $8.25 billion, has taken a similar approach with several drugs. Valeant has been forthright about its goal of maximizing profits for shareholders while minimizing research-and-development (R&D) costs; the company currently spends 3% of its total revenue on R&D. Rodelis Therapeutics, a private company with little public transparency, also became notorious for buying the rights to cycloserine — a niche medication used in multidrug-resistant tuberculosis — and immediately increasing its price by more than 2000%. In response to a negative public reaction, Rodelis has since sold the drug back to its previous owner.

Many factors contribute to high pharmaceutical prices, including drug shortages, supply disruptions, manufacturer consolidations, and R&D costs. Though some companies that have purchased and increased the price of niche medicines cite R&D as an

**Table 1. Price Increases Affecting Off-Patent Medications on the WHO Model List of Essential Medicines.***

| Drug | No. of Manufacturers | Primary Indication | Year of FDA Approval | Price Increase (%) | Year of Price Increase† |
|---|---|---|---|---|---|
| Pyrimethamine (Daraprim) | 1 | Toxoplasmosis | Before 1982 | 5433 | 2015 |
| Dactinomycin (Cosmegen) | 1 | Multiple cancers | Before 1982 | 3437 | 2006 |
| Cycloserine (Seromycin) | 1 | Multidrug-resistant tuberculosis | Before 1982 | 2248 | 2015 |
| Albendazole (Albenza) | 1 | Echinococcus, neurocysticercosis | 1996 | 1920 | 2010–2013 |
| Flucytosine (Ancobon) | 2 | Cryptococcal meningitis | Before 1982 | 1864 | 2005–2014 |
| Procarbazine (Matulane) | 1 | Hodgkin's lymphoma, brain cancers | Before 1982 | 1537 | 2004 |
| Praziquantel (Biltricide) | 1 | Schistosomiasis, other parasitic infections | 1982 | 356 | 2015 |
| Chlorambucil (Leukeran) | 1 | Chronic lymphocytic leukemia | Before 1982 | 334 | 2012–2015 |
| Penicillamine (Cuprimine) | 1 | Wilson's disease, cystinuria | Before 1982 | 300 | 2015 |
| Sodium nitroprusside (Nitropress) | 1 | Severe hypertension | Before 1982 | 212 | 2015 |

* Data on the year of FDA approval are from the FDA Orange Book; data on price increases are from Micromedex.
† Years expressed as a range indicate that the price increased each year.

explanation for high prices, it's hard to find credible evidence of their involvement in substantial drug-development projects. Turing and Amedra state on their websites that they're engaged in research, yet neither company lists substantial R&D activities or publications. Frequent license sales, mergers, and acquisitions obscure the financial picture. This complexity and lack of transparency in the pharmaceutical market enable companies to remain vague about the reasons behind increasing prices.

What makes this business model particularly disturbing is that vulnerable patients — such as immigrants, refugees, and people of low socioeconomic status — are often disproportionately affected, since many of the medications are for tropical or opportunistic infections. These patients often have limited or no access to insurance, or have access only through public programs, so already stark health disparities are compounded. In addition to pyrimethamine, albendazole, and cycloserine, other antiinfective medications that are often used in treating vulnerable patients have also had dramatic price increases. These include two drugs that are the first-line agents in their respective classes: praziquantel (Biltricide), used for schistosomiasis and other parasitic infections, and flucytosine (Ancobon), used for cryptococcal meningitis.

We believe that other older medications on the WHO Model List of Essential Medicines may be potential targets for opportunistic companies using this business model. Many of these drugs lack therapeutic alternatives, target conditions that contribute to high morbidity and even mortality, are produced by one or few manufacturers, and exist in a market that offers little incentive for new entrants. The WHO recommends that items on the Model List "be available within the context of functioning health systems at all times in adequate amounts . . . and at a price the individual and the community can afford."[3]

***Many drugs on the WHO Model List of Essential Medicines lack therapeutic alternatives, target conditions that contribute to high morbidity and mortality, are produced by one or few manufacturers, and exist in a market that offers little incentive for new entrants.***

**Table 2. Essential Medicines at Risk for Price Increases.***

| Drug | No. of Manufacturers | Indication | First-Line Therapy | Year of FDA Approval |
|---|---|---|---|---|
| Quinidine gluconate, intravenous | 1 | Severe malaria | Yes | 1989 |
| Rifapentine (Priftin) | 1 | Tuberculosis and latent tuberculosis | Yes | 1998 |
| Rifabutin (Mycobutin) | 3 | Tuberculosis in some patients with HIV–AIDS | Yes | 1992 |
| Pyrazinamide | 2 | Tuberculosis | Yes | Before 1982 |
| Capreomycin (Capastat) | 1 | Tuberculosis | No | Before 1982 |
| Streptomycin | 1 | Tuberculosis | No | 1998 |
| Aminosalicylic acid (Paser) | 1 | Tuberculosis | No | 1994 |
| Ethionamide (Trecator) | 1 | Tuberculosis | No | Before 1982 |
| Pentamidine, inhaled (NebuPent) | 1 | Pneumocystis prophylaxis | No | 1989 |
| Pentamidine, intravenous (Pentam) | 1 | Pneumocystis treatment | No | 1984 |
| Sulfadiazine | 1 | Toxoplasmosis | Yes | 1994 |
| Ivermectin (Stromectol) | 2 | Onchocerciasis, strongyloidiasis | Yes | 1998 |
| Clofazimine (Lamprene)† | 1 | Leprosy | Yes | 1986 |
| Dapsone | 2 | Leprosy, pneumocystis treatment, toxoplasmosis prophylaxis | Yes | Before 1982 |
| Paromomycin | 2 | Leishmaniasis, cryptosporidiosis, intestinal amebiasis | Yes | 1997 |
| Benznidazole | 1 | Chagas' disease | Yes | Not approved |
| Permethrin 5% cream | 3 | Scabies, lice | Yes | 1989 |

* Data on the number of manufacturers are from Micromedex; data on the year of FDA approval are from the FDA Orange Book.
† Currently available only under investigational new drug status.

Although many of these drugs may be at risk for price increases, antiinfective agents appear to be the most vulnerable.

We identified 17 antiinfective medications on the WHO list that are produced by three or fewer manufacturers and have limited or no therapeutic equivalents (see Table 2). Seven of these treat tuberculosis; others are first-line treatments for leprosy, strongyloidiasis, malaria, or Chagas' disease. We speculate that these medications may experience dramatic price increases in the future, which would disproportionately affect vulnerable populations in the United States. Ironically, many of these agents are among the least expensive medications available elsewhere; price-control mechanisms not available in the United States, such as governmental ability to negotiate drug prices, are the primary reason for this discrepancy.

As questionable as the actions of companies such as Turing and Valeant may seem, they don't violate antitrust laws. Even in cases in which anticompetitive behavior is suspected, the Federal Trade Commission (FTC) has been slow to respond or has failed to prove that the company's behavior was anticompetitive.[4] Recently, the FTC began investigating a "restricted drug distribution scheme" by Turing that may limit access to potential generic-drug entrants. A congressional committee is investigating the actions of Valeant, Rodelis, and Retrophin.

Timely market solutions that promote competition are needed when high prices result from monopolies. Currently, there's little incentive for a generic drug company to enter a niche market, especially given the expensive and lengthy process of gaining approval from the Food and Drug Administration (FDA). One recent development has been the FDA announcement that it will expedite the review of abbreviated new drug applications for generic entrants when only one manufacturer exists. This move may encourage potential generic entrants that would otherwise have little incentive to enter a niche drug market with limited sales. In addition, the FDA could consider eliminating user fees in

order to encourage competition in drug markets threatened by limited sales and small profit margins.

One private-sector response has come from compounding pharmacies, which have recently started providing cheaper versions of many drugs that have become prohibitively expensive. Compounded drugs are not subject to FDA approval, and some observers have suggested that the agency consider temporary approval in order to ensure access to essential medicines.[5] Although this approach may help individual patients, it's unlikely to represent a market-wide solution, since compounding pharmacies won't provide access to all essential medicines, have limited capacity, and are not universally available. In addition, because most insurance plans don't cover compounded drugs, the out-of-pocket expenses for patients can be high, further exacerbating disparities.

We believe that empowering Medicare to negotiate drug prices and opening U.S. markets to imported drugs would be a welcome regulatory response.[5] Quality and safety could be ensured by reliance on reputable regulatory agencies such as the European Medicines Agency and Health Canada. Other globally accepted regulatory mechanisms, such as the WHO guidelines designed to ensure that drugs are produced using acceptable manufacturing and laboratory practices, could also be used.

Until U.S. regulatory leaders and policymakers consider creative proposals for addressing socially detrimental incentives in drug manufacturing and pricing, pharmaceutical companies will continue to grow wealthy at the expense of taxpayers and vulnerable patients. Meanwhile, providers are left prescribing medications that they know are unaffordable, relying on options other than first-line therapies, or assisting patients in acquiring medications through alternative, unregulated sources.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMp1601559


HISTORY OF MEDICINE

# The Great War and Modern Health Care

Beth Linker, Ph.D.

Nearly a century after the United States entered World War I, we can appreciate more than ever its profound effect on medical practice. For many people, World War I conjures up images of men with shell shock, trench foot, and influenza. The burden of these conditions hastened the development of a host of new medical specialties as well as the construction of many hospitals and clinics. For these reasons, some historians believe World War I was responsible for ushering in modern medicine and the modern hospital.[1] An equally important — yet often overlooked — part of this history was the establishment of rehabilitation medicine, a specialty that helped pave the way for the eventual creation of the Veterans Administration.[2]

Six months after the United States declared war on Germany in April 1917, Congress passed the War Risk Insurance Act. Buried amid its actuarial language about insuring ships and soldiers' next of kin was a guarantee that all disabled soldiers would receive "rehabilitation and re-education," making the care of disabled soldiers a federal mandate that would be paid for with federal dollars. For the first time in U.S. history, the Army Medical Department recognized rehabilitation medicine as a necessary branch of its health care delivery system.