COMMENTARY

THE AMERICAN JOURNAL of MEDICINE®

The 'Invisible Hand' Doesn't Work for Prescription Drugs

Pharmaceutical innovation has been responsible for many "miracles of modern medicine." Reliance on the "invisible hand" of Adam Smith to allocate resources in the market for prescription drugs, however, has had a number of adverse consequences.[1] Prescription drugs in the US are not only high in price relative to international price benchmarks, but their use often diverges from objective efficacy and cost-effectiveness. Examples include US Food & Drug Administration (FDA) approval of costly drugs like Aduhelm based on biomarkers with limited or no information on clinical and cost-effectiveness; pricing of drugs like insulin and enzalutamide (sold as Xtandi) in the US at several multiples of the price in other countries; FDA approval of a variety of highly priced "me-too" drugs like anti-programmed cell death protein 1 (PD-1) monoclonal antibodies with a low percentage of therapeutic advantage and no reduction in price as more drugs enter the market; significant evergreening of drug patents based on slight modifications that have limited therapeutic advantage but which may be more convenient; and markedly increased utilization of drugs due to physician marketing and direct-to-consumer advertising. Moreover, the high profitability of drugs for the treatment of cancer and rare diseases has led to a relative underemphasis of drug development for general medical conditions affecting larger patient populations. The Inflation Reduction Act (IRA) contains provisions that should favorably impact some aspects of drug pricing, but the intended effects may be blunted. The objectives of this Commentary are to explain how these intertwined problems are rooted in market imperfections and propose solutions that would improve the match of utilization with efficacy and cost, while fostering continued innovation.

Funding: None.

Conflicts of Interest: None.

Authorship: Both authors had access to the data and a role in writing this manuscript.

Requests for reprints should be addressed to David S. Guzick, MD, PhD, Emeritus Professor, University of Florida School of Medicine and Dentistry, Gainesville, FL, 32605.

E-mail address: dguzick@ufl.edu

https://doi.org/10.1016/j.amjmed.2022.11.022

As applied to prescription drugs, the assumptions underlying a well-functioning market imply that consumers have complete and accurate knowledge of the efficacy, safety, and side effects of an array of drugs treatments. Under this construct, consumers make rational choices about the price they are willing to pay for a drug subject to their assessment of its value (taking into account benefits and risks) and their income. Supply and demand are independent, that is, demand for a drug is not influenced by the manufacturers who supply it. To the extent that producers profit from the sale of a drug, frictionless entry of other drug producers into the market can occur. Under classic economic theory, the resultant downward pressure on price reduces long-term profits toward zero.

This depiction of how Adam Smith's invisible hand guides the price and utilization of prescription drugs under a free market is so far from reality as to be fantastical. This is because none of the assumptions of a well-functioning market applies to prescription drugs:

- At a time of significant illness, the emotional state of patients and their families and their lack of knowledge and expertise limit their ability to make rational, informed choices about potential drug treatments. Instead, patients generally rely on their physicians.
- Patients do not make purchasing decisions based on the true price of a drug because their out-of-pocket cost is usually only a small fraction of the price paid to the manufacturer.
- Physicians often cannot draw on comparative-effectiveness data in counseling patients because of gaps in the literature.
- Physicians' recommendations may be influenced by drug company marketing and their own income objectives.
- When a safe and effective drug is commercialized by a pharmaceutical company, entry of other manufacturers is constrained by patent protection. Patents serve an important societal purpose—a quid pro quo in which a time-limited monopoly is awarded for new drugs to encourage research and development, balanced in the long-term by postpatent societal benefits. However, drug companies have fostered regulations through lobbying

and litigation that are favorable to patent evergreening and high prices that, in practice, are not subject to reduction by competition with other manufacturers of similar drugs.
- Supply and demand are not independent. Producers can create demand through physician marketing and direct-to-consumer advertising.

These deviations from the underlying assumptions of a competitive market produce imperfections in the production, consumption, and price of prescription drugs. Moreover, when public and private health insurance covers more than 90% of the population, as is now the case in the US, insurance benefits take on characteristics of public goods.[2] That is, once a prescription drug becomes a covered benefit for everyone in a plan, individuals cannot effectively be excluded from the use of the benefit, and one individual's use of the benefit does not reduce its availability to others.

Supply-demand analysis works for private goods that meet underlying competitive assumptions; the analogous framework for public goods is cost-benefit analysis, guided by the principle that society's collective resources should only be used if benefits outweigh costs. In practice, as an alternative to cost-benefit analysis of medical treatments—made difficult by the need to attach a dollar value to benefits that include the saving or prolonging of life—cost-utility analysis (CUA) is used by the National Institute for Health and Care Excellence (NICE) in the UK and by similar entities in other countries.

In the US, federal policy paralysis regarding comparative effectiveness and CUA of prescription drugs has adversely impacted the quality of care, price, and utilization.[3] *Quality* is compromised by limitations in the funding of comparative effectiveness studies that are needed by physicians to make optimal treatment decisions. Indeed, efficacy determination by the FDA is almost always based on a randomized controlled trial that compares the drug being evaluated with placebo but not with a standard-of-care drug, should one exist. *Prices* of drugs are elevated because once the FDA grants approval, drug companies can set high launch prices; this will not change under the IRA. When patents are granted for drugs similar to ones that already exist, there usually is little in the way of price reduction relative to the competition because the industry follows a price leadership model.[4] Manufacturers net a high percentage of their list price after being filtered through a complex system of wholesalers, pharmacy benefit managers, pharmacies, insurers, and patient rebates.[5] The incentives in this byzantine structure motivate continued high launch prices for new drugs and subsequent price increases, although the latter is a less important consideration than the launch price.[6] *Utilization* of drugs is enhanced by low out-of-pocket patient cost and by supplier-induced demand in a setting wherein cost-effectiveness and cost-utility information on alternative treatments is limited.

To improve the quality of care pertaining to prescription drugs, reduce their price, and foster appropriate utilization while continuing innovation, a number of actions can be taken within the existing framework of the US health care industry. FDA policies and procedures could be externally reviewed and updated with the objective of identifying approaches that could reduce the complexity, time, and cost to manufacturers of obtaining approval for new drugs and indications, without sacrificing the rigor of safety and efficacy evaluation. Assessment of a new drug by the FDA could be based on a clinical trial that incorporates a standard-of-care drug, should one exist, as a treatment arm. Federal funding for independent comparative effectiveness and CUA studies could be increased accordingly. As is the case in other countries, an independent panel could review the comparative effectiveness and CUA evidence for proposed drugs and make recommendations to the Centers for Medicare & Medicaid Services (CMS) about formulary inclusion. The virtually unique international circumstance of direct-to-consumer advertising could also be reconsidered.

The IRA provides a framework for CMS negotiation of drug prices, but its practical effects are potentially blunted by the long duration of patent protection before price negotiation kicks in, by higher launch prices and by inevitable lobbying and litigation. Moreover, many high-profile drugs that are be currently eligible for price negotiation under IRA rules would not be eligible in 2026, the first year of implementation. Significant dedicated effort among a wide cross-section of stakeholders will be needed to ensure the intended effects of the IRA. Annulment of the ability of CMS to negotiate drug prices by an electoral change in Congress must also be considered.

In summary, the US cannot rely on the invisible hand to assure both continued pharmaceutical innovation and cost-effective use of prescription drugs. Subject to political will, however, solutions are available to help achieve this goal.

David S. Guzick, MD, PhD[a,b]
Eli Y. Adashi, MD, MS[c]
[a]*Dean Emeritus, University of Rochester School of Medicine and Dentistry, Rochester, NY*
[b]*Former President, UF Health, University of Florida, Gainesville*
[c]*Professor of Medical Science, Former Dean of Medicine and Biological Sciences, Brown University, Providence, RI*

References

1. Smith A. The Wealth of Nations. Hollywood, FL: Simon & Brown; 2011:4:279.
2. Cohen RA, Martinez ME, Cha AE, Terlizzi EP. Health insurance coverage: early release of estimates from the National Health Interview Survey, January-June 2021. Available at: https://www.cdc.gov/nchs/data/nhis/earlyrelease/insur202111.pdf. Accessed November 21, 2022.

3. Patashnik EM, Gerber AS, Dowling CM. *Unhealthy Politics: The Battle Over Evidence-Based Medicine*. Princeton, NJ: Princeton University Press; 2017.
4. Rosenthal E. Why competition won't bring down drug prices. *New York Times* June 21, 2018; . Available at https://www.nytimes.com/2018/06/21/opinion/competition-drug-prices.html [Accessed November 21, 2022.
5. Guzick DS. *An Introduction to the US Health Care Industry: Balancing Care, Cost and Access*. Baltimore, MD: Johns Hopkins University Press; 2020:384–90.
6. 46Brooklyn Research. Drug price increases have slowed, but new analysis shows launch prices pushing costs into orbit. Available at: https://www.46brooklyn.com/research/2019/10/11/three-two-one-launch-rfmyr. Accessed November 21, 2022.