The Ethics and Economics of Pharmaceutical Pricing

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Annu. Rev. Pharmacol. Toxicol. 2015. 55:191–206

First published online as a Review in Advance on August 13, 2014

The *Annual Review of Pharmacology and Toxicology* is online at pharmtox.annualreviews.org

This article's doi: 10.1146/annurev-pharmtox-010814-124649

Keywords

drug access, patents, innovation, differential pricing, price controls, rationing, prescribing

Abstract

The cost of drugs is a major and rapidly rising component of health-care expenditures. We survey recent literature on the ethics and economics of skyrocketing pharmaceutical prices and find that advances in economic research have increased the sharpness and focus of the ethically based calls to increase access by modifying patent protection and reducing prices. In some cases, research supports ethical arguments for broader access. Other research suggests that efforts to broaden access result in unintended consequences for innovation and the medical needs of patients. Both ethicists and economists need to be more cognizant of the real clinical settings in which physicians practice medicine with real patients. Greater cross-disciplinary interaction among economists, ethicists, and physicians can help reduce the disjunction between innovation and access and improve access and patient care. This dialogue will impact private industry and may spur new multistakeholder paradigms for drug discovery, development, and pricing.

INTRODUCTION

The tension between patient access to medicines and the high drug costs needed to create incentives for innovation has occupied considerable policy and scholarly attention for a quarter century, beginning in the 1990s with the introduction of intellectual property protection in the World Trade Organization and reaching a crescendo in the 2000s with the controversy over high prices for HIV/AIDS drugs (1). More generally, the juxtaposition of ethical considerations with the economic realities of modern health care has provoked intense discussion. We survey recent literature in twelve areas of health-care policy in which these tensions between economic and ethical imperatives arise. Recent economic research has increased the sharpness and focus of the ethically based calls to increase access by modifying patent protection and reducing prices. In some cases, the research supports ethical arguments for broader access. In many cases, however, research suggests that efforts to make the marketplace more ethical by broadening access result in unintended consequences for innovation and otherwise work against the medical needs of patients.

EMPIRICAL RESEARCH CORROBORATING THAT DRUGS ARE SPECIAL GOODS WHOSE VALUE IS NOT CAPTURED BY THE MARKETPLACE

Half a century ago, in his seminal work on the economics of medical care, Kenneth Arrow (2, p. 950) responded to another economist who had written that "a time *may come* when medical ethics will have to be considered in the harsh light of economics" by saying, "Of course, this expectation amounts to ignoring the scarcity of medical resources; one has only to have been poor to realize the error. We may safely assume that price and income do have some consequences for medical expenditures." If we accept that "there seems to be little room for the unequal distribution of a vital commodity such as health care in a just society" (3, p. 621), few would argue that our current system—in which the poor have significantly less access than the wealthy to medical care, including pharmaceuticals—is ethical (4).

Ethicists argue that drugs are special goods different from other marketplace commodities and that pharmaceutical companies have an obligation to make drugs available to patients who cannot pay the profit-maximizing patent monopoly prices such companies charge (5). Recent economic research corroborates this view by demonstrating that patients place a much higher value on medical services and drugs than their ability to pay would suggest (6). For example, the value people put on an additional year of life ($110,000–150,000) is beyond their ability to pay, even in rich countries (7). For reference, median annual household income in the United States is $53,046 (8).

A corollary finding is that copayments and coinsurance reduce adherence for medically necessary pharmaceuticals among low-socioeconomic-status patients (9–11), whereas reducing prices improves adherence and medical outcomes (12, 13). A Kaiser Family Foundation and Harvard School of Public Health survey found that 29% of respondents had not filled a prescription because of cost, and 23% cut pills or skipped doses to make the medication last longer (14). A 2012 Consumer Reports survey found that 33% of respondents with pharmaceutical benefits and 59% of respondents without benefits had taken some (non-physician-sanctioned) action to save money on their prescriptions. The most common of these, as in the Kaiser survey, was skipping filling a prescription (45% of those without and 18% of those with pharmacy coverage). Other actions included skipping a scheduled dose or cutting pills in half (15).

UNINTENDED CONSEQUENCES OF POLICIES INTENDED TO INCREASE ACCESS IN LESS DEVELOPED COUNTRIES

Limited access to expensive drugs developed for rich-country markets is compounded by the availability problem, i.e., the limited research and development (R&D) funding for diseases affecting less developed countries (LDCs) exclusively (16). In 2000, the United Nations adopted a Millennium Development Goal to, "in cooperation with pharmaceutical companies, provide access to affordable essential medicines in developing countries" (17).

Although they acknowledge that drug patents can be justified by both utilitarian and property rights principles, some ethicists argue that the "most basic rights. . .of life, liberty, and/or the right not to be harmed" should "override property rights. . .such as during crises such as the threat of death by HIV/AIDS" (18, p. 599). Others argue that pharmaceutical companies are for-profit entities, and it is unfair to hold them responsible to pursue socially beneficial but unprofitable endeavors (such as producing unprofitable drugs) when no other firm or individual is held to such a standard (19, 20). Nonprofit pharmaceutical companies have emerged as an alternative to traditional markets or institutions, one that is more effective at addressing basic human needs (21).

Compulsory Licensing

One policy response to the ethical mandate to increase access in LDCs is compulsory licensing, which allows "governments to issue production licenses for [Intellectual Property] protected innovations that are needed to respond to public emergencies," such as the AIDS pandemic in Africa (22, p. 1109). Some argue that compulsory licenses reduce the incentive for pharmaceutical companies to invest in drugs for diseases likely to be subject to compulsory licensing, thereby reducing R&D for diseases and regions with the greatest medical need (22). Others contend that compulsory licensing is on the decline because drug companies can threaten to withdraw their products from a given market (23). Although official compulsory licensing has declined, non-licensed manufacturing—outside of the UN-sanctioned process—continues to flourish in India, from which firms export generic versions of patented HIV/AIDS drugs to LDCs (24, 25).

Differential Pricing

To address calls for increased access, some drug companies employ differential pricing, i.e., selling in different countries at different prices to reflect the income level of each country (22, 26–29). The ability to engage in such nation-by-nation price discrimination requires significant market power (30). Much of the literature in the 1990s concerned parallel importation—distributors in countries with lower drug prices reselling pharmaceuticals to countries with higher prices (31, 32). More recently, Morel et al. (33) compared average pharmaceutical prices across 14 countries and found multiple instances of higher-income countries facing lower average prices than lower-income countries, suggesting that differential pricing alone will not ensure affordable access unless LDCs also gain market power.

UNINTENDED CONSEQUENCES OF GOVERNMENT EFFORTS TO CONTROL DRUG COSTS

In some cases, countries that impose price ceilings (either directly, as in Canada, or indirectly, as in Germany) to increase patient access may deter market entry for drugs (34). High prices may price out a large section of the population, but some economists argue that price controls

may effectively price out an entire country. Thus, although overall life expectancy is higher on average in Europe, European cancer survival rates are lower than the US survival rate (35). For example, the 5-year survival rate for men over age 75 diagnosed with prostate cancer is 92.1% in the United States but only 64.4% in Scotland (36). Between 2004 and 2008, the US Food and Drug Administration (FDA) approved 59 anticancer drugs, of which 46 were also approved in Europe. Every US payer that was studied covered all FDA-approved drugs, whereas in Scotland, only 43% of licensed drugs were covered (37).

In reference pricing, regulatory agencies, governments, or insurers set a single reimbursement price for a cluster of similar drugs. The price may be an average of all drugs in the cluster or equal to the lowest-priced drug (38, 39). Patients are responsible for paying the difference if they choose a higher-priced product (40). Reference pricing exerts significant downward pressure on prices for both branded and generic drugs, resulting in lower effective copayments (41). Reference pricing may also, however, create unintended consequences by discouraging innovation within existing classes of drugs (42) and by providing a reference point for manufacturers to collude on prices (43).

These unintended effects may extend to physician prescribing as well. For instance, because of skyrocketing cancer treatment costs, US Medicare and Medicaid reimburse for cancer drugs at the average sales price, plus 6% markup, to cover practice costs. This creates an incentive for physicians to use costlier drugs, because 6% of generic drugs is so low—sometimes below the cost of administration. Some may ask, "Why use paclitaxel (and receive 6% of $312) when you can use Abraxane (for 6% of $5,824)?" (44, p. 1654).

Both physicians and economists have recently called for value-based pricing rather than reference pricing in the United States as well as the United Kingdom (45–47). Value-based pricing is intended to keep costs down while increasing incentives for pharmaceutical firms to develop innovative products. Reference pricing raises concerns because it is based on broadly defined therapeutic classes that understate the value of new and innovative drugs (42). However, even value-based pricing can distort incentives for clinical research. Bristol-Myers Squibb (BMS), for example, developed a new drug to treat melanoma. The improvement in life expectancy averaged 4 months, but 20% of patients experienced 18 months additional life expectancy, whereas 80% of patients gained 2 weeks or less. There was no way to determine which patients would benefit and which would not, and BMS had no reason to try to identify them in the future. If they used biomarkers to determine the relevant patient population, those 80% of patients who would see no substantial benefit would cease to buy the drug, slashing BMS's revenues (48). This paradoxical economic disincentive to identify biomarkers has important implications for the personalized or precision medicine paradigm that aims to more directly target specific drugs to individual patients.

DRUG SHORTAGES

Shortages have become a significant problem in drug delivery. Injectable and antihypertensive drugs, antibiotics, anesthetics, and muscle relaxants are all affected drug classes. Shortages may be temporary (e.g., due to inaccurate estimations of demand or manufacturing problems) or permanent (e.g., when a patent expiration causes prices to fall below sustainable profitability) (49, 50).

Some drug shortages arguably stem from well-intentioned attempts to introduce ethical considerations into pricing. For example, demand for injectable oncology drugs does not contract simply because prices increase—cancer patients will continue to need treatment, regardless of the price. Pharmaceutical companies could, hypothetically, deal with a shortage by raising their prices, pricing out some of their poorer patients and restoring equilibrium. Although most pharmaceutical companies do not raise prices in response to a shortage (and thereby price out the poor),

such shortages can lead to a gray market in which distributors buy as much of the product as possible, then sell it back to health-care providers at an enormous markup from the original price (49). One 2011 analysis of the gray market found an average markup of 650%, with a maximum markup of 4,533% for labetalol, an injectable antihypertensive drug (51). As noted below (see the section titled The Effectiveness of Patents in Providing Incentives for Drug Discovery), perverse incentives created by patent protection can also contribute to drug shortages.

FINANCIAL ASSISTANCE PROGRAMS: EQUITABLE DISTRIBUTION OR PUBLIC RELATIONS SCHEME?

The problem of access is exacerbated by income inequality, which results in more patients being priced out of access to medicines (52). This is particularly interesting given that, on average, the unit price falls with higher income inequality in the case of other products (53), thereby lending additional credence to the ethical view that drugs are special market goods.

Pharmaceutical manufacturers tout financial assistance programs as a response to access inequity created by income inequality. Financial assistance is theoretically a win-win situation in that it increases industry profits by introducing price discrimination and expands access for those who would otherwise be priced out (48). One study found assistance programs helped improve glycemic and lipid control (54), suggesting such programs are potentially useful. However, the public relations benefits for drug companies may outstrip the actual improvement in medical outcomes for patients. As of 1999, companies offered some form of patient assistance program for 53% of the 200 most-prescribed medications in the United States (55). But a large-scale survey of Medicare patients (in 2006, immediately after the launch of Medicare Part D) found that only 1.3% of seniors reported participating in a patient-assistance program. One survey found that only 4% of such programs reported how many patients their assistance programs served, and 53% did not disclose their income-eligibility criteria (56). Clinics surveyed about the use of patient assistance reported that fast-changing eligibility requirements and unreasonable income-documentation requirements were barriers to using such programs more widely (57).

A potential barrier to more widespread adoption of these programs may simply be logistics. One study found that applying to a patient-assistance program consumed, on average, 12 h of pharmacist time and 99 h of other staff time per month (57). For some programs, new applications must be submitted for every medication request, including refills.

The Robert Wood Johnson Foundation, the Pharmaceutical Research and Manufacturers of America, and patient advocacy groups have developed websites to help patients find financial assistance. Other nonprofit groups (e.g., MedBank of Maryland) have developed services to centralize and streamline the application and fulfillment process (58).

EFFECTS OF DIRECT-TO-CONSUMER ADVERTISING ON PRICING AND ACCESS

Direct-to-consumer advertising (DTCA), which is legal only in the United States and New Zealand, has become the fastest-growing segment of pharmaceutical marketing following changes in FDA regulations on broadcast advertising (59). Nevertheless, as of 2012, DTCA accounted for only 11.4% of total pharmaceutical marketing expenditures, a figure far surpassed by marketing to physicians (60).

The ethical concerns about DTCA are that it lowers the price elasticity of demand, increases demand through inappropriate prescriptions, and allows the producer to increase prices and thereby reduce access, all without a corresponding benefit in health-care outcomes (61, 62). As Hoffman & Wilkes (63, p. 1302) write, "If [doctors] believe that patients want and expect drugs

then doctors will prescribe them even when they know they are not indicated, even when patients don't specifically ask for them, and even when an individual patient never expected the drug but the doctor thinks he or she did. All that is required for direct to consumer advertising to increase product sales dramatically is that some patients ask and that doctors begin to believe that many patients will be dissatisfied without it" (63).

Balotsky (30) argues that for some lifestyle drugs, such as Viagra or sleep aids, it may be appropriate for advertising-induced demand increases to lead to price increases. For essential drugs, however, he argues that rising prices could result in negative health outcomes as a result of restricting access according to patients' economic status. However, one empirical study failed to demonstrate that DTCA results in higher prices (64), suggesting that further study is necessary to establish a connection between DTCA and reduced access.

MEDICARE PART D, MEDICAID, AND OTHER FORMS OF CONSUMER BARGAINING POWER

Superior bargaining power enables hospitals to obtain substantial discounts relative to drug stores, even large chains, in procuring antibiotics (65). Similarly, Medicare Part D created value for patients, not only by expanding pharmaceutical access through wealth transfers but also by increasing bargaining power. Duggan & Scott Morton (66) point out that the increase in insurance coverage should make patients less price-sensitive and thereby increase prices; however, Medicare Part D is administered through private insurers that have used their ability to restrict the market share of pharmaceuticals (via formularies) to bargain with drug manufacturers. This ability to control demand gives insurers substantial bargaining power vis-à-vis the suppliers of patented drugs (67). In fact, use of pharmaceuticals increased while average prices fell in the first year of the program (66), and the effect persisted over time (67). This finding is particularly noteworthy because at the time Medicare Part D came into effect, many economists, physicians, and policy makers were concerned that the prohibition against Medicare as a whole bargaining collectively on behalf of all insurance companies would cede too much bargaining power to pharmaceutical companies.

Duggan & Scott Morton (68) had found earlier that Medicaid's market share increased prices in a given market. Medicaid accounted for 19% of all pharmaceutical spending at the time of the study, suggesting the potential for market power. However, Medicaid reimbursement is set at a fraction of the average cost to non-Medicaid patients, thereby creating a substantial incentive for pharmaceutical manufacturers to increase the price charged to non-Medicaid customers. Studies of pharmacy benefit managers (PBMs) and restrictive formularies have found similar price-shifting behaviors (69–71).

The price-shifting externalities associated with bargaining power raise novel ethical questions. Rather than drugs being allocated according to need, access is enhanced by the might-makes-right market power of the patient's representative. A powerful PBM may lower prices for its own patients but may indirectly increase the prices charged to other patients.

ORPHAN DRUGS, INNOVATION, AND PRICING

Even the wealthiest patients cannot afford to underwrite R&D for a rare disease (72). Although a disease that affects fewer than 200,000 individuals is considered rare (and includes such well-known rare diseases as multiple sclerosis or cystic fibrosis), most affect far fewer individuals. Overall, 7,000 rare diseases affect 6–7% of the developed world (73). With such tiny volumes, even at extremely

high prices, orphan drugs are unlikely to be manufactured absent monetary incentives beyond those of the market (74). Only 10% of patients with rare diseases have a treatment available (75).

Orphan drug legislation provides economic incentives complementing the ethical motivation to treat rare diseases (76). The United States, European Union, Japan, and Australia have programs to encourage drug development for rare diseases; these programs guarantee 5–10 years of marketing exclusivity and regulatory fee waivers, and all except Australia offer additional tax credits and grants for R&D costs (77, 78).

Between 1983 and 2010, at least 14 drugs were recycled as orphan drugs—that is, they had previously been discontinued but were made available again after the US Orphan Drug Act (ODA) was passed (79). Although Wellman-Labadie & Zhou (79) imply that this is a failure of the ODA, it is in fact precisely what this type of legislation should aim for—increasing access to drugs that would otherwise be unavailable. The ODA has led to a 69% increase in the annual flow of new clinical trials for long-established rare diseases (80).

With no practical alternatives, orphan drugs command high prices (81). One study found 11 had annual sales totaling over $100 million and that 9% of orphan drugs have blockbuster status (sales over $1 billion) (79). This raises classic resource allocation questions regarding the ethics of paying high prices to treat a small group when those funds could provide better health-care outcomes for larger groups.

Rare disease subsidies also create agency problems by creating perverse incentives for drug manufacturers to game the system. These subsidies may encourage disease stratification—variously referred to as Trojan applicants, salami slicing, or the more technical ODA-qualifying subdivisions—in which manufacturers artificially divide a common disease into several rare diseases (81). In particular, recent advances in pharmacogenomics (the interaction of a pharmaceutical with an individual's genetic makeup) have allowed pharmaceutical companies to "genetically subdivide diseases that affect a large portion of the population into groups small enough to qualify for orphan drug status" (82, p. 366). Such subdivisions account for half of total ODA R&D (83).

THE EFFECTIVENESS OF PATENTS IN PROVIDING INCENTIVES FOR DRUG DISCOVERY

Patent law allows drug companies to charge high prices over the life of a patent, creating incentives for new discoveries that become more broadly available at lower generic prices once the 20-year term of the patent expires (84, 85). However, recent studies have called into question whether patents actually increase innovation (86); some have even found that they have a negative effect on innovation (87, 88). Notwithstanding the doubts this patent puzzle raises, in the particular case of drug development, some policy mechanism is necessary to recoup the rising costs of R&D and, in particular, clinical trials that constitute 80% of the initial fixed cost of drug development (89).

Patents and clinical trial expenses can create incentives for firms to prioritize drugs that require shorter clinical trials. For example, because late-stage cancer drugs have a shorter required clinical trial than early-stage cancer drugs, their effective patent lives are longer. Thus, there is greater incentive for firms to target R&D on late-stage cancer, even though more lives could arguably be saved by focusing on early-stage treatments (90).

Patent protection can also contribute to drug shortages. For example, the FDA approved levoleucovorin, a cancer drug, in 2008. It is the *l*-isomer of leucovorin, a cancer drug that has been available since 1952. It was no more effective than its parent molecule, but because it cost 52 times more, manufacturers switched to this much more lucrative product. Eight months after levoleucovorin's introduction, there was a widespread shortage of leucovorin (44).

EFFECTS OF PATENT EXPIRATION ON PRICES

Some studies have confirmed the expected result that generic entry pushes branded prices down (91–93), whereas others have found the opposite effect (94–96). In 1984, the Hatch-Waxman Act was passed to increase the use of generic drugs in the United States, in part by allowing generic manufacturers to challenge existing patents. These generic patent challengers target the most profitable drugs, effectively shortening the life of the patent (97, 98). However, the effective patent life of branded drugs is no shorter after the act's passage than it was before (99). Nevertheless, patent challenges transfer significant value to consumers. For example, a comprehensive study of hypertension drugs in the United States found that patents challenging generic drugs saved consumers $92 billion, whereas branded producers lost about $14 billion (100). An analysis of the 10 highest-volume therapeutic classes in Medicare Part D found that generic entry reduced prices, lowering seniors' average daily cost of therapy from $1.50 per day in 2006 to $1.00 per day in 2010 (101). The effect for other patients is likely to be even larger because seniors (along with out-of-pocket spenders) pay the highest prices for both generics and branded drugs (96).

The fact that a drug goes off patent does not necessarily lead to low prices for patients, even when governmental procurement prices for generics are low (52, 102). Some companies have sought to avoid the price-reducing impact of patent expiration by shifting production to a single stereoisomer of an existing drug, thereby sustaining revenues with no improvement in therapeutic outcome. The leucovorin example referenced above is one example of such behavior. Cameron et al. (102) found that wholesale markups in the private sector were as high as 380%, and retail markups rose to 552%.

Sweden introduced a reform requiring pharmacists to substitute the cheapest available generic (or cheapest product imported from a country with lower pharmaceutical prices) unless the physician explicitly opposes generic substitution. A study (95) found that after the reform, prices of branded drugs facing generic competition fell by 14%; even the prices of brands that did not face generic competition fell by 10%. The average effect of introducing generic competition on branded prices was only −0.45% before the reform and decreased to −4.78% afterward. These results suggest that pharmacists and physicians play a crucial role in creating competitiveness in pharmaceutical markets and saving money for patients (see the section titled The Role of Physicians).

ALTERNATIVE MECHANISMS CREATE INCENTIVES FOR INNOVATION WHILE ENHANCING ACCESS

In light of the apparently poor performance of patents in serving medical needs and industry's continuing and knowing reliance on highly inefficient, wasteful, and costly clinical trials, some researchers have pioneered more ethical and economically efficient alternative mechanisms for spurring innovation (103). Collaborative efforts such as the nonprofit Alliance for Clinical Research Excellence and Safety as well as the industry-driven TransCelerate initiative have reimagined R&D systems and approaches that could reduce the cost and time required to bring a new drug to market, thereby benefiting patients, industry, and investors. Such multistakeholder initiatives have the collateral benefit of fostering regulatory innovation (104).

Kremer & Williams (105) propose prizes or prize-type mechanisms, such as advanced market commitments in which the prize is conditional on the existence of demand in a given market. A proposed government-funded global Health Impact Fund would, instead of a patent, grant registrants a share of the contribution made to the global health outcomes of all registered products. Registrants would also be required to sell the medicine wherever it is needed at no more than the lowest feasible cost of production and distribution and, after the end of the reward period, offer

free licenses to generic manufacturers (106). This idea has not yet been implemented or evaluated in the literature.

Building on the idea that the primary costs of development lie in the clinical trial and review process, which some deem a public good (89), Ridley et al. (107) propose that companies should receive a priority review voucher (PRV) when they develop an FDA-approved therapy clinically superior to existing treatments in treating a neglected disease. They would be required to forgo patent rights on and find a manufacturer for the therapy. The voucher could be used to expedite the review of another drug under development or could be sold on the open market. The authors estimate the voucher would be worth more than $300 million for a potential blockbuster drug. The United States adopted this voucher system in 2007. In a 2011 survey of pharmaceutical companies, 91% of respondents with PRV-eligible therapies reported that the availability of the voucher was a strong or major consideration during the process of initiating or continuing a neglected disease project (108), suggesting this incentive has been quite successful.

In one of the boldest initiatives to address the problem of underserved LDC markets, the Global Alliance for Vaccines and Immunization (GAVI) launched an Advanced Market Commitment initiative in 2009 to promote the development of pneumococcal disease vaccines (109). Sponsors agree to fully or partially finance the purchase of qualifying vaccines for poor countries, at a prespecified price, up to a fixed number of individual immunizations. Once the predetermined number of treatments has been purchased at the specified price, manufacturers must either sell further treatments at a low, affordable price in the long term or license their technology to other manufacturers to create price competition (110). Even with sponsor subsidies, evidence suggests that resulting prices remain unaffordable in LDCs (111). Some argue that drug companies have eluded the intention of the GAVI initiative by therapy switching rather than devoting resources to the development of breakthrough therapies (112). Nevertheless, with backing from the Bill & Melinda Gates Foundation and the cooperation of the United Nations Children's Fund (UNICEF), the World Health Organization, and the World Bank, GAVI appears to have the staying power to help ameliorate the LDC availability problem outlined above (see the section titled Unintended Consequences of Policies Intended to Increase Access in Less Developed Countries).

THE ROLE OF PHYSICIANS

Although the Hippocratic Oath binds physicians to be the agents of their patients medically, physicians often neglect, or are simply unaware of, their role as economic agents for patients. Physicians play a crucial role in controlling prices and enabling patients to access affordable therapies. As noted in Arrow's seminal work on the economics of medical care, cited above (see the section titled Empirical Research Corroborating That Drugs Are Special Goods Whose Value Is Not Captured by the Marketplace), patients generally do not have sufficient medical knowledge or information to evaluate the value of pharmaceuticals; this information "is precisely what is being bought from most physicians" (2, p. 946). Because efficient pricing in any market, including pharmaceuticals, depends critically on the ability of consumers to evaluate the utility of products they consume, patients can make rational decisions to maximize utility only with the guidance of their physicians. The Internet has changed this dynamic somewhat, as patients can now walk into a doctor's office with information unthinkable a generation ago, although the role of the physician as the gatekeeper of demand persists.

There is insufficient appreciation for the economic role of physicians, in part because physicians are not themselves adequately informed. Surveys have found that the majority of physicians inaccurately estimate the true cost of drugs (113). In the absence of explicit efforts by hospitals, insurers, or the pharmaceutical manufacturers to inform physicians, the latter tend to overestimate the cost

of inexpensive drugs and underestimate the cost of expensive drugs (114). In some specialties, physicians have incentives to increase drug prices, most notably in oncology, in which more than half of practice revenues come from chemotherapy sales (44). A study of metastatic breast cancer found that increasing a physician's profit on a drug by 10% increases the likelihood of prescribing that drug by 11–177%, even after controlling for clinical indicators and physician experience (115). This phenomenon occurs outside the practice setting as well. One study found a significant relationship between the market share of drugs and their profitability for pharmacies (116).

Some argue that an ethical conflict arises when physicians give any weight to economic considerations because an incentive to control costs is effectively the same as an incentive to provide less care for their patients (117). This idea became prominent during the rise of managed care in the 1990s. Shortell et al. (118, p. 1103) contend that "while fee-for-service medicine encourages the physician to continue providing services until the incremental benefit is equal to the patient's cost (which is often as low as zero after meeting deductibles), capitated payment provides incentives for a physician to use fewer resources in patient treatment. . . . The physician becomes a double agent representing both the interests of the patient at hand and those of the organization and all enrollees." Although widely cited, this argument is erroneous because the assumption that the cost of care for patients is near zero is false. In fact, 92% of insured workers in the United States have a tiered cost-sharing plan for prescription drugs (119) that, as noted above, is nontrivial for a large number of patients. Moreover, the full cost of drugs is ultimately passed on to patients through premium increases (120). Thus, physicians must continually take patient costs into account, even in fee-for-service contexts.

Pharmaceutical companies recognize the role physicians play in regulating demand. All else being equal, some physicians are more likely to prescribe a generic drug, whereas others are more likely to prescribe a branded drug (121). Such preferences among prescribing physicians and pharmacists explain a significant share of the variation in generic substitutions (122). The vast majority of promotional spending goes to detailing, samples, and other forms of promotion targeted toward physicians, with only a fraction going to DTCA (60, 123). This promotion is not intended solely to convey information and has a strictly persuasive effect on physicians' prescribing (124). Furthermore, the majority of physicians are unable to recognize when information presented by pharmaceutical companies is inaccurate (125). The vast majority of research has associated physician exposure to information from pharmaceutical companies with higher costs and prescribing frequencies and lower prescribing quality (126).

Some lawmakers, physicians, researchers, and individual patients mistakenly believe that, "sooner or later, care will need to be explicitly rationed" (127, p. 1489). In fact, care has always been rationed because, like all resources, medical goods and services are limited and must be allocated in some manner. Rising prices and premiums serve to ration care by forcing poorer patients, or those who place less value on health care, to consume less. Studies have also long shown that, although physicians consider prescription costs for uninsured patients, they rarely extend the same cost-consciousness to insured patients (122, 128) and that pharmaceutical companies price their drugs accordingly (129). Nevertheless, it is fair to say that physicians are not aware how cost considerations affect their patients, even if the latter are insured. Exhibiting such price consciousness would have a twofold effect. First, the cost-quality trade-off would ensure rational patient spending in the short term. Second, rational patient spending would enhance competition in the long term; this has been demonstrated to both enhance innovation and reduce prices (85).

CONCLUSION

The major theme emerging from this review is that the ethics and economics of drug pricing are far more complex than they at first appear. The ethical literature would benefit from greater

appreciation of economic realities, and, conversely, economists can better focus their studies by displaying greater sensitivity to ethical concerns. Both fields need to be more deeply immersed in the real clinical settings in which physicians practice medicine with real patients. Greater cross-disciplinary interaction among economists, ethicists, and physicians can help to reduce the disjunction between innovation and access and improve access and patient care. As this dialogue takes place, it will have an enormous impact on private industry and may result in new multistakeholder paradigms for drug discovery, development, and pricing.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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